

Thesis on

EXPERIMENTAL AND CLINICAL OBSERVATIONS

ON TRANSFUSION OF BLOOD.

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by

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## I N T R O D U C T I O N .

My object in writing a thesis on transfusion of blood is to record the experimental and clinical observations which I have made on the subject during the last five and a half years. The preliminary work included a series of experiments on the technique of blood-vessel surgery and on the methods required for transfusion of blood in animals. Observations were made also on the value of transfusion in the treatment of the constitutional effects of haemorrhage. My clinical observations are based on forty-six transfusions in a series of thirty-nine cases. Different Methods of transfusion have been tried and the details of the operations and of the instruments used will be described. The cases which were treated by transfusion are arranged in the following four groups:-

- I. Cases of Primary or Secondary Haemorrhage - ten cases.
- II. Cases of Secondary Anaemia - six cases.
- III. Cases of Purpura Haemorrhagica - two cases.
- IV. Cases of Pernicious Anaemia- twenty-one cases.

As no description of transfusion would be complete without a reference to former methods, I have considered/



considered it advisable to preface my own observations with an account of the history and progress of the subject.

Most of the experimental work has been done in the Department of Surgery; but I am indebted to Sir Edward Schäfer for permission to perform certain of the experiments upon transfusion of blood in the Department of Physiology, and to Professor Lorrain Smith for permission to operate, and to keep some of the animals, in the Department of Pathology.

Seven of the clinical cases were operated upon by Professor Thomson, and I have to thank him for the opportunity of observing his cases and of recording the facts.

To many of the physicians of the Royal Infirmary, and particularly to Professor Gulland and Dr Boyd, I am indebted for the free use of their notes of both private and hospital cases, and for the opportunities afforded me of performing transfusion.

I have to record my indebtedness to Mr Norman Dott for suggestions regarding the design of the instruments used for indirect transfusion.

I wish to thank Mr Frank W. Pettigrew, Technical Assistant to the Surgery Department, for the photographs reproduced here, and Mr J. T. Murray for the remaining illustrations.

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## Volume II.

### Clinical Records of Cases Treated by Transfusion.

## HISTORY.\*

The early history of transfusion has been studied by Ore, and is recorded in his monograph<sup>1</sup> on the subject.

From his historical researches, it is apparent that transfusion was known to the ancient Egyptians, and had been practised by them. References to transfusion are also made in the classical writings of Pliny, Celsus, and Ovid, who says in his "Metamorphoses". "Why now do ye hesitate and do nothing? Unsheathe your swords and draw the old blood, that I may fill the empty veins with the blood of youth".

The earliest case of transfusion referred to in literature is that of Pope Innocent VIII, in 1492, a description of whose case is given in Villari's "Life of Savonarola". "The vital powers of Innocent VIII rapidly gave way; he had for some time fallen into a kind of somnolency, which was sometimes so profound that the whole court believed him to be dead. All means to awaken the exhausted vitality had been resorted to in vain, when a Jew doctor proposed to do so by transfusion, by a new instrument, of the blood of a young person, an experiment which had hitherto/

\* For the facts regarding the History of Transfusion I am chiefly indebted to the writings of Landois, Crile, Guthrie and McClure and Dunn.



hitherto only been made in animals. Accordingly, the blood of the decrepit old pontiff was passed into the veins of a youth, whose blood was transferred into those of the old man. The experiment was tried three times, and at the cost of the lives of three boys, probably from air getting into their veins; but without any effect to save that of the Pope".

Considerable doubt is thrown upon the veracity of the above statement, as, according to entirely different accounts, the three boys were bled until they died, and the Pope then drank a draught prepared from their blood without any benefit.

The discovery of the circulation of the blood by Harvey suggested to Francesco Folli the following observation written in 1652. "I have read William Harvey's book, which treats of the movement of the heart and of the blood. - This reading, with some ideas I had on the grafting of plants, gave rise in my mind to this third problem, that, the circulation of the blood existing, it would be possible to perform transfusion, by means of which one would not only cure, but rejuvenate and make robust".

Harvey's discovery undoubtedly stimulated interest in the possibilities of transfusion, and shortly/



shortly after the middle of the 17th century numerous experiments were carried out, and the first clinical applications of transfusion were made and recorded. The interest aroused at this time in the possibilities of transfusion is shown by the following quotation from the diary of Samuel Pepys.

"November 14, 1666, Dr Croone told me, that, at the meeting at Gresham College to-night, which, it seems, they now have every Wednesday again, there was a pretty experiment of the blood of one dog let out till he died, into the body of another on one side, while all his own ran out on the other side. The first died upon the place. The other very well and likely to do very well. This did give occasion to many pretty wishes, as of the blood of a Quaker to be let into an Archbishop, and such like; but, as Dr Croone says, may, if it takes, be of mighty use to man's health, for the amending of bad blood by borrowing from a better body".

In 1665, Richard Lower, of Oxford, successfully performed transfusion in animals, and in January 1667, he published the first detailed account of the operation. His experiments showed that an animal which had been bled to the point of death could be resuscitated by transfusion with the blood of another animal/

animal of the same or of a different species. The transfusion was accomplished by means of quills which were tied into the carotid artery and jugular vein of the respective animals. A quill was also fixed in the peripheral end of the jugular vein, in order to withdraw the blood necessary to deplete the animal which was to receive the transfusion. The ends of the quills were stopped with wooden plugs till the preliminary stages of the operation were completed. Finally the animals were tied closely together, and the anastomosis was made by joining together the quills, and, if necessary, by interposing one or more additional quills according to the length of tube required. When the transfusion was started, the stopper was removed from the quill in the upper part of the jugular vein so that the recipient was bled simultaneously. By roughly comparing the amount of blood transfused with the amount lost by bleeding, the animal was kept in good condition while the donor was bled to death. Lower describes further the use of metal tubes for transfusion in the following paragraph.<sup>2</sup>

"Instead of a Quill, take a small crooked Pipe of Silver or Brass, so slender that one end may enter a Quill; and having at the other end, that is to enter/

enter into the vein and artery, a small Knob, and for the better fastening them to it with a Thread; for this is much more easy to be managed than a Quill." Certain of Lower's observations were of special interest, such as the transfusion of a dog for acute anaemia following splenectomy, and the cure of a mangy dog in ten days after transfusion with blood from a healthy dog. In addition to performing the first experiments, Lower, with the assistance of Dr Edmund King, was the first in England to apply transfusion to man. This was on November 3rd, 1667.

According to Landois,<sup>3</sup> the patient in this case was a young man of twenty-two, suffering from some form of mental disturbance. The patient was first bled to the extent of six or seven ounces, and was then transfused with nine or ten ounces from the carotid artery of a lamb. The connecting medium was a long silver canula, and it was noted at the time that the pulsation of the carotid was communicated to the patient's vein. During the transfusion, the patient smoked and drank wine, and at the conclusion expressed himself as feeling well. Several weeks later the operation was repeated, but on this occasion a febrile reaction followed the transfusion. It was reported two years later that the patient's mental condition was unaltered by this novel treatment.

Prior/

Prior to this case, Jean Baptiste Denys had the distinction of performing the first definitely accredited transfusion in man. Before operating, Denys performed experiments on animals, following the methods practised by Lower; Denys transfused both from vein to vein, and from artery to vein. His first patient was a young man reduced to a very low condition by repeated bleeding and purging. After withdrawing three ounces of blood from the patient's vein, nine ounces of arterial lamb's blood were injected, and it is recorded that the patient recovered. In another case, the operation was performed in a more or less healthy man as an experiment, without harmful effect. A third patient suffering from insanity is reported to have been restored to his normal condition for a period of three months, after the transfusion of nine ounces of calf's blood. A second attempt was made to transfuse the same patient, but the operation had to be abandoned, as there was no flow of blood on opening the vein. The patient died shortly afterwards, and Denys was accused of having caused his death. The circumstances of the case brought the operation of transfusion into disrepute in Paris; and a decree was passed forbidding the transfusion of blood in man without the approval of the Faculty of Medicine in Paris. "As a result of this decree, interest/



interest in transfusion was discouraged, and it was almost forgotten by all but a few observers till early in the nineteenth century." (Crile).<sup>4</sup>

In other countries, interest in transfusion was stimulated about this time by the work of Lower and Denys. In Italy, Carsini and Magnani repeated experiments on similar lines. Magnani in particular succeeded in resuscitating dogs bled to the point of death; and further, he recorded the occurrence of haematuria and death resulting from similar experiments in which the dogs had been transfused with lamb's blood. As in France, the operation of transfusion soon met with opposition, and was forbidden by law. At a somewhat later date, similar work was repeated in Germany.

There is little progress to be recorded in the eighteenth and early part of the nineteenth centuries. Occasional references are made to transfusion in the writings of the times, but few experiments or operations on man were attempted.

Experiments were carried out by Rosa, with the assistance of Scarpa the anatomist, in 1783, from which he concluded:-

- (1) That injection of serum alone would not revive an animal bled to the point of death.
- (2) That resuscitation could be accomplished in this condition by transfusion of blood from an animal of/



of a different species, and that the mixture of different bloods was not harmful.

The latter observation was not finally controverted till nearly a century later although, in the interval, many surgeons had expressed a contrary opinion.

A new point which Rosa recorded was that the total amount of blood could be increased by transfusion to a considerable extent without harmful effects.

It is recorded that in 1792 Harwood, the Professor of Anatomy at Cambridge, repeated Lower's experiment, and that in the same year Rosa claimed to have cured a boy said to be suffering from hydrophobia by bleeding the patient and then transfusing lamb's blood. Aveling states that Tardy and Harwood recommended vein to vein transfusion; and this led to the attempt to provide some motive power for propelling the blood. Primitive efforts in this direction were made by Boehm, who employed a piece of duck's intestine as a connecting limb between the two canulas inserted in the veins, and Colluzzi made use of a small bladder placed between the two canulas for the same purpose. It is not surprising that, with such inadequate instruments, the operation of transfusion aroused little enthusiasm.

There was little interest in transfusion until it was revived by James Blundell<sup>5</sup> in 1818. The idea of/

of transfusion was first suggested to Blundell by the death of a woman from post partum haemorrhage.

Recognising the difficulties of successfully performing the operation, he carried out in the first place a series of experiments, which marked a distinct advance in the conduct and status of the operation.

His conclusions may be summarised as follows:-

- (1) Dogs bled till the pulse and respiration were abolished could be resuscitated by transfusion. If the transfusion were delayed for more than five minutes, recovery did not take place.
- (2) The use of a syringe did not interfere with the value of the transfusion.
- (3) Venous blood was as effective as arterial blood.
- (4) Much less blood was sufficient to reanimate the animal than the amount lost by bleeding.
- (5) Dogs could be resuscitated by human blood, but the animals died later.
- (6) Injection of a moderate amount of air into a vein did not cause death.
- (7) If blood was rapidly collected and injected with a syringe there was little risk of clotting.

Prior to this, transfusion was usually performed by the use of canulas from vein to vein, and Blundell was the first to modify the technique by the use of a syringe. In his experiments, the blood was collected/

collected in a cup, and injected by a syringe through a canula fixed in the recipient's vein. Later he employed a more complicated instrument which he called an "impellor".

The results obtained by Blundell in his clinical cases were not at first encouraging, as he had five successive failures: but subsequently he performed transfusion in man with considerable success.

In 1821 Prevost and Dumas demonstrated that defibrinated blood could be used as a substitute for unmodified blood, and they also made some experiments with drugs to delay clotting before transfusion.

During the subsequent years, there was much discussion regarding the best method of transfusion, although there were still differences of opinion as to the comparative value of whole blood, defibrinated blood, and the blood of lower animals.

#### Transfusion with Blood from an Animal of a different Species.

The question of the value of transfusion of blood from an animal of a different species was hardly raised prior to the nineteenth century. In Landois's monograph<sup>3</sup> on Blood Transfusion, many instances are quoted in which lamb's blood had been transfused into human patients; and this form of transfusion was/

was not infrequently employed - chiefly by German surgeons - as late as 1874;.

Much of the early evidence regarding this question was contradictory. Nuck, writing in 1714, had expressed his disapproval of transfusion of animals' blood in man, but Rosa and other writers on the subject did not discriminate between human blood and the blood of animals for this purpose. Blundell, on the other hand, had observed that dogs transfused with human blood after profuse bleeding invariably died within a few days, although they might be temporarily resuscitated. Prevost and Dumas expressed a similar opinion, and stated in 1821 that animals transfused with dissimilar blood, even although the corpuscles were of the same shape, showed little improvement, and seldom survived longer than six days. They observed also that birds injected with mammalian blood died quickly with symptoms suggestive of irritation of the central nervous system. Bischoff, in 1845, rather confused the issue by distinguishing between the effects of transfusing birds with defibrinated and with unmodified blood. He concluded from his experiments that defibrinated dissimilar blood had no injurious effect, whereas unmodified dissimilar blood was rapidly fatal. He also distinguished between the toxic action of venous and arterial

. mammalian/



mammalian blood when injected into birds, stating that the former only was injurious. With other observers, however, he found that exsanguinated animals could only be restored by transfusion with similar blood.

Magendie, in 1842, observed that the blood corpuscles of birds or of frogs disappeared immediately on injection into mammalian blood, and similarly that mammalian blood could not be detected after injection into the circulation of birds.

Brown-Séguar, in 1858, confirmed these facts. He noted the presence of the oval corpuscles widely distributed in the blood in different parts of the body, but that within an hour of transfusion, all the foreign corpuscles had disappeared. The same observer, however, contradicted his former statement by reporting that he could detect mammalian corpuscles intact in the circulation of birds several weeks after transfusion.

Panum, writing in 1863, confirmed the views of Blundell, Magendie, Brown-Séguar, and others - that transfusion with dissimilar blood was useless and dangerous. He definitely stated that the blood of animals should not be used for transfusion in human cases. He found that dogs transfused with lamb's or calf's blood after being exsanguinated died shortly after//



after the injection, even in cases where temporary improvement had followed transfusion. He attributed the fatal effects to the destruction of the foreign corpuscles. Landois, in 1875, showed that the addition of animal's blood to human blood was followed by swelling of the human red corpuscles and liberation of the haemoglobin. He observed further that the leucocytes lost their amoeboid movements and showed other signs of death. Schäfer, in 1879, concluded that transfusion with blood of any of the lower animals could not produce any benefit in man; and that the mixture of dissimilar bloods was likely to be followed by the most dangerous results. According to Schäfer, the danger of transfusion with foreign blood is due both to the destruction of red corpuscles, and to the action of the foreign blood upon the walls of the blood vessels and other living tissues. The liberation of haemoglobin within the blood plasma produces bloody urine, ecchymoses in different parts, and a tendency to thrombosis and embolism. The action of the foreign blood upon the white corpuscles further indicates that such blood acts as a poison to all the living tissues.

The observations of Panum, Landois, and Schäfer finally settled the question of transfusion with dissimilar blood; and there is now no reason to alter/

alter the opinions expressed by these observers. Although numerous cases have been recorded in which animal's blood was transfused into the human circulation without a fatal effect, and in some of which benefit was described as having followed the operation, there are, according to Schäfer, the strongest possible reasons for doubting the latter claim; and it is probable that in such cases the patients have recovered in spite of, rather than as a result of, the transfusion. The small amount of blood injected in many of the non-fatal cases probably explains why disastrous results did not ensue.

#### Transfusion of defibrinated blood.

One of the chief difficulties and risks of transfusion has been the tendency of the blood to clot, and thus prematurely to bring the operation to a conclusion; or, later, to produce dangerous or even fatal symptoms by intravascular thrombosis or embolism.

Prior to 1821, unmodified blood alone was injected, if one excludes a few cases in which anticoagulant substances had been employed. A new field was opened up about this time by the researches of Dumas and Prevost, who proved experimentally that defibrinated blood could be successfully employed for resuscitating exsanguinated animals. Dieffenbach, in/

in 1828, Bischoff in 1835, and Müller in 1838, confirmed these observations, but the clinical application of this fresh discovery, which excluded the risk of gross clotting of the blood, was seldom considered; and prior to 1860, only thirteen cases of transfusion with defibrinated blood had been recorded.<sup>7</sup>

Magendie, in 1842, described various sequelae after transfusion with defibrinated blood, such as the appearance of blood-stained froth at the nose and mouth, oedema and congestion of the lungs, subpleural haemorrhages, swelling and congestion of the mucosa of the stomach and intestine, and intestinal haemorrhages. These symptoms were explained by Magendie as being due to alteration in the viscosity of the blood by removal of the fibrin.

Panum, in 1863, strongly recommended the use of defibrinated instead of whole blood. He observed symptoms similar to those described by Magendie in his experiments, but did not consider their occurrence to mean anything more than simple rupture of capillaries. Ponfick regarded the symptoms as due to irregularities in the mode of injection, and Landois, in 1875 believed that they were the result of blockage and rupture of capillaries by the stromata of the injected corpuscles.

Kohler, in 1877, threw further light on the subject/

subject by noting the occurrence of widespread capillary thrombosis after transfusion with defibrinated blood, especially in the capillaries of the lungs and intestinal mucosa. Kohler further observed that the tendency to thrombosis was much greater when the blood was allowed to coagulate spontaneously, and the clot was compressed, instead of preparing the blood by whipping in the usual way to remove the fibrin.

Maldovan,<sup>8</sup> in 1910, found the transfusion of rabbits with freshly defibrinated blood caused death in every case, with coagulation of the blood in the heart and large vessels.

Briot, Jouan, and Stoub<sup>9</sup> in 1911 found that in the rabbit a dose of even 10 cc. of defibrinated blood was toxic when injected intravenously, if the time between defibrination and injection did not exceed ten minutes. After this time the result is uncertain, but twenty minutes after defibrination as a rule no harm results. The authors further stated that defibrinated plasma is also toxic, though less so than defibrinated blood. From these facts they concluded that the toxic product is due to the phenomena of coagulation.

Hédon<sup>10</sup> also experimenting with rabbits, found that defibrinated blood was toxic if injected soon after preparation, and that such an injection was constantly fatal if the animal had lost much blood. Death/



Death preceded by convulsions frequently occurred suddenly during the transfusion. When the quantity of transfused blood was moderate in amount, the animal sometimes survived, with or without temporary symptoms; but even under these conditions death was frequent.

When a post mortem is done at once, clots may be found in the right side of the heart, and in the venae cavae, but in some cases only a small filiform clot may be found in the inferior vena cava. In other cases there is no trace of clotting or thrombosis, the blood is fluid throughout and there may be nothing to explain the cause of death. Moldovan suggests that such reactions are due to anaphylaxis.

The time factor is apparently an important one with regard to the toxicity of defibrinated blood, at any rate in the case of rabbits. According to Hédon, the toxicity is much reduced twenty or thirty minutes after the withdrawal of the blood, and small doses can then be safely injected, if the rabbit has not previously been bled, but it is still sufficient to kill a rabbit which has been bled freely. If left for several hours at ordinary temperature, or better for twenty-four hours at a low temperature, defibrinated blood will largely lose its toxic characters, while retaining its restorative power. Rabbits transfused with defibrinated blood preserved for some/



some hours recover, but may still present temporary symptoms.

The addition of citrate of soda was found by Hédon to reduce the toxicity of defibrinated blood. From his experiments, Hédon concludes that defibrinated blood should only be employed for transfusion if it has been kept for some time, and if citrate of soda in the proportion of 3 gm. of citrate to 1000 cc. of blood is added. It will be noted that this amount of citrate of soda is sufficient by itself to prevent the coagulation of the blood.

While these experiments indicate that dangerous symptoms are liable to follow transfusion with defibrinated blood, it must be noted that the rabbit appears to be much more liable to develop toxic symptoms than other animals such as dogs.

Experimental evidence suffices to explain the varying results which have been recorded by those who have employed defibrinated blood as a means of treatment.

Hunter<sup>7</sup>, writing in 1889, quotes several cases of anaemia in which serious symptoms followed injection of small quantities of defibrinated blood, the amounts varying from 50 cc. to 100 cc.. The symptoms noted included collapse, rigors, vomiting, diarrhoea, nephritis, and haemoglobinuria.

Howe<sup>11</sup>, //

Howe,<sup>11</sup> prior to 1889, claimed to have transfused successfully both with defibrinated and whole blood, but considered that his results were better when the latter was used. Morawitz<sup>12</sup> was favourably impressed with the results from transfusion with defibrinated blood, but, like most of those who have used this form of blood, the amounts injected were usually small. In spite of his enthusiasm, Morawitz found it necessary to advise against transfusion with defibrinated blood while the blood was still warm. Thus, clinically, the importance of the time factor, suggested by the experiments of Moldovan and Hédon, is confirmed.

Both the clinical and experimental evidence suggest that in using defibrinated blood, some toxic factor is introduced which is absent when unmodified blood is employed. Hunter,<sup>7</sup> in 1889, stated that "The great feature of defibrinated blood in all cases, however obtained, is the uncertainty of its action. It is sometimes quite harmless, at other times highly dangerous, this result being entirely independent of the quantity injected, or the care taken in injecting it." Compared with other methods of transfusion, the preparation of defibrinated blood is certainly more troublesome; and there is the further objection that a considerable proportion of the blood is lost in the process. Morawitz obtained 200 cc. of blood for/

for injection from a total amount of 250 cc. withdrawn from the donor;

In recent years, the use of defibrinated blood has been almost wholly abandoned in favour of whole blood, and as there is no obvious improvement that could be made, either as regards its preparation or the method of its injection, it seems unlikely that indications for its use will again arise.

For twenty years prior to the publication of Crile's<sup>4</sup> recent work on transfusion, in 1909, the operation of transfusion made little progress, and, although occasional cases were recorded, comparatively few surgeons were in favour of it. The introduction of the infusion of normal saline for the treatment of shock and the constitutional effects of haemorrhage provided a safe and more or less satisfactory substitute for transfusion. The prejudice against transfusion of blood and in favour of normal saline is expressed by Littlewood<sup>13</sup>, who remarks that attempts to transfuse blood, either by the direct method or after defibrination, were difficult, of doubtful value, and sometimes positively dangerous, and in his experience the infusion of saline was much safer. Hunter further expressed the views commonly held at this time in recommending saline instead of blood, the/

the only indication for which he admitted to be sudden and severe haemorrhage.

The indifferent results which the early workers on transfusion obtained was largely due to the fact that "the greater part of transfusion as formerly performed was done crudely and empirically before the development of bio-chemistry, physiology, pathology, and bacteriology to a degree at all approaching the present state of development". (Crile)<sup>4</sup> It must be remembered also that prior to Lister's work in 1865 - 1870 transfusion, like all other operations, was attended by the risk of subsequent sepsis; Even in 1892, John Duncan<sup>14</sup> referred to a case of fatal septicaemia following transfusion, and to two other cases in which sepsis had complicated the patient's recovery.

The greater certainty of asepsis, the use of preliminary tests for detecting incompatibilities of the patient and donor, and improved instruments and technique, have been responsible for the increased popularity and the extended application of transfusion in recent years..

Methods/



# Methods of Transfusion Employed prior to 1909 (Crile)<sup>4</sup>.

Till the last decade, the methods used were adapted for the transfusion of blood in three forms:-

- (1) Unmodified blood.
- (2) Defibrinated blood.
- (3) Blood rendered incoagulable by the addition of salts.

## (1) For unmodified blood.

The blood was usually transfused from vein to vein, or from artery to vein. Landois recommended<sup>3</sup> direct arterial transfusion, either in a peripheral or central direction. Schäfer<sup>6</sup> in 1879, investigated the different methods of transfusion, and from experimental evidence was of the opinion that transfusion from artery to vein was perfectly safe, and rapidly effectual. He particularly recommended, however, centripetal arterial transfusion in cases where the patient was in extremis, and failure of the heart was momentarily expected. In such an emergency, he believed that direct arterial transfusion would yield brilliant results, even in cases in which the heart had ceased to beat while the operation was being effected, and he doubted whether resuscitation might not be effected from the connection/

connection of the two arteries. It is interesting to note that Blundell also regarded this method of transfusion favourably in cases of apparent death from bleeding. The chief advantage of centripetal arterial transfusion for cases of impending heart failure following haemorrhage is the rapid improvement of the blood supply of the heart itself through the coronary arteries consequent upon the increased blood pressure.

The early transfusions performed in the seventeenth and eighteenth centuries were made by a simple arrangement of tubes between the donor and recipient, as in the method of Lower previously described.

The primitive methods of propelling the blood from vein to vein were improved on by Blundell, in 1818, when he invented a new apparatus in which the blood was first collected in a cup by means of a syringe.

In 1826, Scott,<sup>15</sup> employed an apparatus which consisted of a syringe connected by flexible tubes to the canulae in the donor's and recipient's veins. The blood was thus alternately withdrawn and re-injected. This method was the precursor of many of the modern methods employed for vein to vein transfusion. Subsequent to this date, many new instruments were introduced, some of them similar in/

in principle to those in use to-day, and all these belong to one of the following four groups:-

- (1) Simple tubes in the form of metal or glass canulae, which directly connected the donor's and recipient's vessels. This type of instrument was based upon Lower's original method of transfusion by quills. One of the most efficient instruments of this class was the combination of two glass canulae joined by rubber tubing, used by Landois. The canulae and tubes were washed through with a solution of sodium carbonate before starting the transfusion.
- (2) A receiver to collect the blood from the donor, and a means of quickly injecting the blood into the recipient's circulation. The apparatus of Blundell was an example of this method.
- (3) A conducting system in direct communication with a syringe or with some other means of pumping the blood from the donor to the recipient. Scott's apparatus was the first instrument of this type, and a later example was that introduced by Aveling, whose instrument consisted of a rubber bulb, connected by rubber tubing with the canulae in the veins of the patient and donor. By an arrangement of stop-cocks the alternate/

alternate filling and emptying of the rubber bulb with blood was facilitated. In this way, blood was aspirated from the donor's vein, and injected by compression of the bulb into the recipient's vein.

- (4) Syringe-canula method; In this method, the blood was withdrawn by a syringe from a canula in the donor's vein, and then injected into the canula in the recipient's vein.

<sup>16</sup>  
Hewitt, tied silver canulae into the veins, and used a simple piston syringe for injection of the blood. Two ounces of blood were withdrawn from the donor as quickly as possible, and injected into the recipient's vein, about one minute being taken for the injection. Hewitt stated that the transfer of blood must be completed within three minutes, to avoid the danger of coagulation. Howe,<sup>11</sup> (1889), used either a rubber or glass syringe for this purpose. Hunter,<sup>7</sup> (1889) who was sceptical as to the value of transfusion, believed that the injection of blood by means of a clean syringe was the safest method.

<sup>17</sup>  
Ziemsson, provided in 1892 a simple and reliable method of transfusion by syringes and canulae. Little notice however was taken of his method till it was revived independently by Lindemann in 1913. Ziemsson/



Ziemsson used three syringes of 25 cc. capacity, and these were filled and emptied in rotation, and each syringe was washed out with salt solution before being used again. Between 200 cc. and 300 cc. of blood were injected on most of the occasions. The results achieved by Ziemsson were undoubtedly excellent, and he proved with his syringe method that a measured amount of blood could be accurately transfused with safety to the patient.

(2) Methods and technique employed in the transfusion of defibrinated blood.

The usual method was to introduce the blood centrally with a funnel and tubing into a superficial vein. Hueter recommended the injection of defibrinated blood peripherally into an artery instead of into a vein, and Landois also advised arterial transfusion, but in a central direction. Hueter's reasons for centrifugal arterial transfusion were that the blood flows more slowly to the heart and that the risks of air embolism and phlebitis were avoided. Landois added the further reason that any minute clots or thrombi, if these happened to be present, would be arrested in the capillaries.

(3)/

(3) Transfusion of blood with phosphate of soda solution.

Although occasional references are made in the early literature to the use of anti-coagulant substances, the only substance which seems to have been used to any great extent for this purpose has been sodium phosphate, the use of which was suggested by Dr Braxton Hicks, and revived by Cotterill in 1883. The addition of sodium phosphate to blood for transfusion was frequently made use of by John Duncan, Cotterill, ~~Brakenridge~~, Affleck, and others of the Edinburgh medical school, in the late eighties and nineties. Writing on the subject of transfusion in 1902<sup>18</sup>, Cotterill stated that immediate transfusion of blood by any form of syringe or instrument, was only mentioned to be condemned, as the risk of inducing clotting was very great; while the difficulty of preventing admission of air was considerable. In reference to the injection of defibrinated blood, the same writer mentioned as one of the disadvantages of the method the large quantity of blood which is lost in the whipping process. Cotterill regarded transfusion of blood with sodium phosphate as much the simplest and safest method available at that time.

It was usual to mix six ounces of blood with two ounces of a 5% solution of phosphate of sodium.

Both/

Both Cotterill and Duncan found that this proportion of sodium phosphate was occasionally insufficient to prevent coagulation, and the former advised that one part of the phosphate solution should be added to two parts of blood. It will thus be seen that this solution had less anticoagulant effect than a 2% solution of sodium citrate, recommended later by Lewishon for the same purpose, and used in the proportion of one part of the citrate solution to nine parts of blood.

The mixture of blood and phosphate solution was injected intravenously by means of a large syringe. John Duncan regarded 30 minutes as the minimum time to be taken in injecting eight ounces of the mixture. Cotterill, on the other hand, considered that ten minutes was sufficient time for the same amount. It was common after injection to observe a rigor, and haemoglobinuria occasionally occurred. Duncan laid great stress on the necessity of slowness in injecting the blood, and attributed various symptoms, such as irregularity of pulse, breathlessness and pain in the back, to neglect of this rule; particularly in cases of pernicious anaemia. Hunter, on the other hand, considered that the use of sodium phosphate for transfusion was not devoid of risk, and believed that the unfavourable symptoms which Duncan/

Duncan had observed were due to capillary thrombosis.

Cotterill and Duncan were most favourably impressed with the value of transfusion, and contrasted the lasting results obtained by this means with the frequently temporary improvement following simple saline infusion. It may be worth noting here that Duncan not only practised transfusion of blood, obtained from a donor, but also sometimes reinfused the patient's own blood in certain cases of serious haemorrhage, when the blood was collected and mixed with sodium phosphate before it could coagulate.

Repeated transfusions in cases of pernicious anaemia were frequently made by different observers, and the results achieved by the method seem on the whole to have been more satisfactory than with any of the other methods employed for transfusion about this time, with the exception of Ziemsson's method of simple injection of unmodified blood, by a series of syringes.

From reading an account of the cases one gathers the impression that reactions shown by symptoms of irregular pulse, dyspnoea, pain in the back, or haemoglobinuria, were rather more frequent than are observed with any of the present well known methods, especially when the small amount of blood injected is remembered. In making this statement, the fact is not forgotten that the preliminary tests for agglutination and haemolysis of the bloods of donor and/



and recipient were not available to those employing the phosphate of sodium or any other method about this time.

Some of the reactions observed after transfusion were no doubt due to incompatibility of the respective bloods, rather than to any fault in the technique of the operator.

There is no doubt that until recent years, the results of transfusion were often uncertain, and occasionally dangerous, although brilliant results, especially in cases of haemorrhage were not infrequently recorded. The medical profession as a whole were sceptical about the value of transfusion, and no single method seemed sufficiently reliable to justify its routine adoption. The practice of transfusion therefore remained chiefly in the hands of enthusiasts. Prior to the revival of the operation, which followed the researches of Crile, the vast majority of surgeons refused to consider transfusion of blood as an alternative to the infusion of normal saline.

In order to avoid the risks of intravascular clotting, certain authorities have attempted to transfuse blood by intraperitoneal or subcutaneous injections, methods which are now only historical.

Recent/

Recent advances in transfusion.

There is no doubt that since 1909 transfusion of blood has been practised more scientifically and with better results than ever before. Although the medical profession has perhaps been somewhat slow in recognising its advantages, and in adopting this practice, especially in this country, the unusual opportunities afforded by the recent war have focused medical attention upon it. Amongst the factors which have played an important part in the better results associated with the operation of transfusion, there should be mentioned in the first place the great improvements in the technique of blood vessel surgery achieved by Carrel, Guthrie, and others, the result of whose work suggested to Crile a certain method for the anastomosis of vessels, for the purposes of transfusion, without risk of clotting. The original method which Crile<sup>4</sup> described in 1909 is now rarely employed, but it was the direct inspiration of all the recent work which has been done in perfecting methods and instruments for transfusion. It can now safely be said that there is a choice of many different methods of performing this operation, all of which are reliable.

The risks have been further diminished by the development//

development of serological tests for ascertaining possible incompatibilities of the bloods of donor and recipient. The risks of haemolysis have been recognised for many years, but the demonstration by Moss<sup>19</sup> in 1910 that individuals could be divided into four groups by studying the action:-

- (a) Of their sera on the corpuscles of other individuals, and
- (b) of the sera of other individuals upon their corpuscles

rendered it possible to select for transfusion a donor, whose blood would neither agglutinate nor haemolyse the corpuscles of the recipient, and, what is still more important, whose corpuscles would not be affected by the serum of the recipient. The preliminary tests were further simplified by the discovery of Moss that isohaemolysins never occurred separate from isoagglutinins. This made it possible to eliminate unsuitable donors by the agglutination test alone.

In the early days of the present revival of transfusion, the technique employed was on the whole rather complicated, but the later tendency has been to revert to the simpler methods. Of the innovations which have widened the scope of transfusion, none has been more productive of fruitful results than/

than the introduction of sodium citrate as an anti-coagulant substance. The sodium citrate method was reported on by three workers almost simultaneously; first by Hustin, of Brussels, in 1914; a little later in America by Weil ; and finally by Lewisohn.

The next notable contribution to the subject of transfusion refers to the preservation of living red blood corpuscles in vitro, which was first worked out experimentally by Rous and Turner in 1916. These observers proved that citrated blood, to which dextrose in isotonic solution had been added, could be preserved without loss of function for several weeks, if kept in the ice chest. They further showed that such cells could be used for transfusion after washing in Locke's solution to which a certain proportion of gelatin had been added. The addition of gelatin was found necessary to protect the cells from mechanical injury during the process of washing before the transfusion. The practical value of the observations of Rous and Turner was proved by the successful results achieved by Robertson, using their methods for the treatment of wounded in France in 1918. Blood previously stored from selected donors was found perfectly satisfactory for the treatment of haemorrhage and shock, and was specially useful when, during an offensive, the number of wounded was so great as to leave no time for the routine selection of a suitable donor.



Recent methods of performing transfusion.

The fresh impetus given to transfusion dates from the publication of Crile's book on Haemorrhage and Transfusion in 1909, in which were published the details of his method of performing direct transfusion. Crile's interest in transfusion was aroused in 1898, but at that time, and for some years later, he failed to find a safe method. The principle on which Crile's method is based is the exact apposition of the intima of the vessels of the donor and recipient. Vessels which are anastomosed in this way remain patent for an indefinite period, without any danger of clotting at the junction. This simple fact was finally demonstrated by the experiments of Carrel and Guthrie in 1905. The application of the methods of blood vessel surgery to transfusion suggested to Crile the lines on which the existing methods could be improved.

In his early experimental and clinical work, the Carrel technique for the end to end anastomosis of blood vessels was followed. An artery of the donor was divided, and directly sutured to the proximal end of the vein of the recipient. In the case of human patients, the radial artery was selected, and joined to a superficial vein of the arm. The results/

results of this method of transfusion proved satisfactory, but the delicate manipulations necessary made the operation one of such technical difficulty that it was scarcely practicable, except in the hands of those with special experience of blood vessel surgery.

Direct apposition of artery to vein by means of a canula or clamp.

In order to avoid the difficulties of suture, Crile introduced a canula for end to end anastomosis with exact apposition of the intima of the vessels of the donor and recipient. The original canula used by Crile is in the form of a short tube with a handle. The inside diameter of the canula varies from 1.5 mm. to 3 mm., according to the size of the artery. In employing the method, the vein of the recipient is pulled through the lumen of the canula, and then cuffed back so that the intima of the vein is exposed, and in this position it is fixed by a single silk ligature. The end of the radial artery, after being gently dilated with a pair of fine artery forceps, is pulled over the vein, and secured by a silk ligature. In this way, the artery and vein are joined, and the intima of the two vessels is continuous. //

continuous. One disadvantage of the Crile canula is that the size of the recipient's vein may render it difficult to pull the vein through the canula without obliterating the lumen. This difficulty was overcome by modifications of the instrument, such as those introduced by Elsberg, Sorresi, and others. In using such an instrument, care is necessary to avoid any traction on the vessels, as this may narrow particularly the radial artery. There is a tendency also for the vessels to be kinked, and the close approximation of the patient's arms makes it difficult to observe whether the flow is continuing or not.

While Crile's original canula is intended for arterio-venous anastomosis, Sorresi's modification is used for vein to vein transfusion, a superficial vein of the donor's arm being joined to the external jugular vein of the recipient. Sorresi transfused successfully with this method in fifty-four cases.

The demonstration by Crile of a certain, though difficult, method of transfusion aroused considerable interest, especially in America. Surgeons in this country were later in reinvestigating the possibilities of transfusion, and practically no interest was taken in the subject till the practice of transfusion was brought to the notice of British surgeons by American and Canadian surgeons serving in France. This fact is referred to by the Lancet, in which it is stated in the leading article of June 1st, 1918, that/

that "We doubt whether any English surgeon could have been found to perform the operation of blood transfusion, even so recently as four years ago." This statement produced a letter from Sir Berkeley Moynihan, who stated that he had performed direct transfusion by Crile's and other methods from 1908 onwards. The writer first performed direct transfusion of blood in 1913.

Arterio-venous Transfusion, with interposition of a canula.

In 1909, Brewer and Leggett introduced the use of a simple glass tube coated with paraffin as a substitute for Crile's type of canula. Pope modified the method by using a rubber tube between two glass canulae, which was a revival of the method used by Landois, with the improvement that the canulae received a preliminary coating of paraffin. Tuffier later used a simple metal tube coated with paraffin. Bernheim, in order to make the process more simple, employed double silver canulae, the two halves of which were tied in separately, and then joined to complete the anastomosis. The writer independently introduced a similar form of canula, the details of which will be described later. These methods for arteriovenous/



arteriovenous transfusion are simpler than the original method described by Crile, and are on the whole satisfactory.

A method in which the radial artery itself is used as a canula is described by Hull,<sup>20</sup> and has been successful in his hands. By means of a traction suture, the radial artery of the donor is drawn through a slit within the recipient's vein. Sauerbruch and Hartwell have also employed methods of slipping the end of the donor's artery directly into the recipient's vein. An objection which is common to all the methods of transfusion in which the radial artery is used is that the amount of blood used cannot be accurately measured, and at the same time the operation puts the donor to more inconvenience than where a superficial vein is chosen. These reasons stimulated efforts to simplify the procedure still further by improvements of the former methods of transfusion from vein to vein. Syringes alone, or syringes directly connected with the canulae, or large paraffin tubes for receiving the blood for injection have been much used for this method of transfusion.

Syringe/

Syringe method of indirect transfusion.

This method had previously been successfully used by Ziemsson, but his efforts had failed to attract much attention, and had been generally forgotten. Lindemann, in 1913, revived the syringe method, but used an improved form of canula, which could be pushed into the vein without incision and with the minimum of damage to the intima. Lindemann recommended that twelve record syringes of 20 cc. capacity should be used in rotation, and that a syringe should not be used a second time until all traces of blood had been removed with normal saline. This method of transfusion has given excellent results in the hands of its author, but the number of syringes and assistants needed is a drawback.

Syringe method with canulae and two-way stop-cock.

The convenience of vein to vein transfusion, which is sometimes practicable without incision of either the donor's or recipient's vein, led to the adoption of several devices based on the principle of a single syringe connected to the canulae by a two-way stop-cock. The best known apparatus of this type is that of Unger, which provides also for the intermittent injection of saline, so that the blood has little time to clot. Clotting within the syringe is/

is also hindered by keeping the barrel cool with an ether spray. Bernheim and others have employed other instruments based on the same principle, and the writer also has tried several forms of this apparatus which will be described later.

#### Transfusion of blood collected in large paraffin tubes.

In 1909, paraffin was first used to delay coagulation during transfusion by Brewer and Leggett, who found that by coating the simple glass canulae the direct transfusion of blood could be satisfactorily carried out. Curtis and Davis found in 1911 that considerable quantities of blood could be collected in a paraffin glass bulb, and that transfusion could be completed satisfactorily before clotting occurred. The advantages of being able to measure the amount of blood transfused was the main consideration which led to the adoption of this method of transfusion, which, although intended in the first place purely for experimental work, has since been applied clinically with satisfactory results. As originally designed, the apparatus consisted of a paraffin-lined cylinder with an opening at its upper end for the attachment of a rubber air bulb, with which a positive or negative pressure could be produced as desired. At the lower end, the cylinder was/

was drawn out into two canular tips, which were directly introduced into the exposed veins of the donor and recipient respectively. In performing the transfusion the blood was alternately aspirated into the cylinder, and forced into the recipient's vein.

Risley and Irving, Kimpton, Hooker and Satterlee, and others, have modified the shape of the cylinder, and the method of using it.

The tube described by Kimpton and Brown<sup>21</sup> is one of the best forms adapted for this method of transfusion. The tube consists of a glass cylinder of varying capacity, closed at the upper end by a cork stopper; at the lower end, the cylinder is drawn out into a canula. There is a side tube which opens into the cylinder just below the upper end. Both the canula and the side tube should face in the same direction, so that when the tube is filled with blood it may if necessary be laid down, or carried with the side tube and tip of the canula uppermost without risk of losing blood. In order to prepare the tube, it must be sterilised and coated with paraffin. A small piece of pure clean paraffin with a melting point of  $50^{\circ}$  C. is placed in the cylinder, and the cork inserted; the apparatus can then be sterilised in the autoclave. While the tube is still hot, the inner surface should be evenly coated with a thin layer of paraffin; the projecting end of the cork and/



and the side tube should also be coated. Finally the excess of paraffin is allowed to run out of the canula, the tip of which may be wiped with a sterile swab to ensure that it remains patent. It is advisable to cool the cylinder as quickly as possible to ensure that the surface is uniformly coated. Some sterile wool should be lightly packed into the side tube so that the air may be filtered when the air pump is used.

With reference to the coagulation time of blood, collected in a paraffin tube, Kimpton and Brown stated that rabbit's blood was found to remain in the tube for eight to ten minutes before beginning to clot.

#### Transfusion with anticoagulants.

The use of alkaline salts for delaying coagulation has been known to physiologists and used by them for many years. Certain of these substances, such as oxalate of soda, are quite unsuited for transfusion, and till recently, the practicability of applying citrate of soda for transfusion does not appear to have occurred to anyone. The proportion of sodium citrate to blood for laboratory work has usually been 1%, and as in this strength only a moderate amount of blood could be transfused without toxic effects, it was//

was not till Lewisohn showed that blood containing .2% of sodium citrate, sufficient to prevent coagulation, could safely be injected in large amounts, that the value of anticoagulant substances for transfusion was finally demonstrated. Reference has already been made to phosphate of sodium, which was used to a considerable extent twenty or thirty years ago. Those who worked with phosphate of sodium found that coagulation could not be safely prevented with less than 1.25% of this salt in the blood. Recent writers on transfusion have overlooked the fact that sodium phosphate was used long before sodium citrate for transfusion.

Leech extract has been proposed as an alternative to alkaline salts in order to keep the blood fluid for transfusion. Lewisohn<sup>22</sup> experimented with the intravenous injection of hirudin, and reported that a dose of 100 milligrams of hirudin caused death in one dog, no ill effects in a second dog, and most alarming post-operative symptoms in a patient, who remained in a precarious condition for over thirty-six hours. Hooker and Satterlee have employed hirudin both experimentally and clinically, and state that the dose used by Lewisohn was much in excess of what they deemed advisable. The latter authors never used more than 7 milligrams of hirudin for/

for transfusing 500 cc. of blood, and in this proportion no ill effects from hirudin were observed in numerous experimental transfusions on dogs. Writing in 1916, Hooker and Satterlee<sup>23</sup> mention fourteen clinical transfusions with hirudin, and thirteen with paraffined pipettes and canulae. Of the thirteen paraffin cases there were no chills or febrile reactions, but six of the fourteen hirudin transfusions were followed by chills and fever; as these unfavourable symptoms appeared only in the cases of the latter half of the hirudin series, they concluded that there was some fault in the hirudin which was used. As their experimental animals had not suffered in any way from transfusions of hirudin blood, they concluded that dogs were either less sensitive to the toxic effects of hirudin, or that the preparations of hirudin sold commercially varied as regards their toxic action.

Apart from the apparent difficulty of obtaining a standardised preparation of hirudin, there are other disadvantages of leech extract which render its application to transfusion unsuitable. Hooker and Satterlee state that it cannot be sterilised by heat without destroying its activity; that it must therefore be prepared under rigidly aseptic conditions; and that it is difficult to keep sterile in solution, requiring the addition of some antiseptic such as thymol.

Sodium Citrate.

Hustin, Weil, and Lewisohn, independently reported on the use of sodium citrate for transfusion. Hustin<sup>24</sup> used citrate in one case mixed with glucose. Weil reported at a meeting of the Academy of Medicine on December 11th, 1914, that he had used sodium citrate successfully, employing 1 cc. of a 10% solution of sodium citrate to 10 cc. of blood. Lewisohn, who was working at the subject experimentally at this time, showed later that this amount of citrate was excessive, and likely to prove toxic in a large transfusion of 1200 cc. Weil made the interesting observation that the immediate effect of transfusion with citrated blood was to lower the coagulation time.

Lewisohn was led to try citrate of sodium in his efforts to find a suitable noncoagulant for transfusion. He first experimented with hirudin, but found that if given in sufficient quantity to prevent clotting, it was apt to prove toxic. In experimenting with sodium citrate, he determined in the first place the minimum amount of the salt necessary to prevent the blood from clotting, and found that sodium citrate must be added to blood in the proportion of .2% for this purpose. Similar results were obtained with both human and dog's blood. A mixture of dog's blood with .2% sodium citrate solution was found to remain fluid for forty-eight hours, but any/



any proportion less than this failed to produce any delay in clotting. Further experiments were made to decide the amount of sodium citrate in solution which could safely be injected intravenously. A dog weighing eleven pounds which was transfused with blood mixed with 15 cc. of a 10% solution of sodium citrate died almost instantaneously. This experiment was repeated twice, with exactly the same result, and Lewisohn<sup>22</sup> therefore concluded that 1.5 gm. of sodium citrate was a fatal dose for a dog weighing 11 lbs. From this observation he concluded that 15 gm. would be a fatal dose for a patient weighing 110 lbs., but as even 10 gm. would nearly reach the fatal limit, it would be impossible to apply this method if the 1% ratio suggested by Weil were used, except for small amounts. Weil mixed 2.5 gm. of sodium citrate with 250 cc. of blood, and therefore the toxic dose would be approached if 1000 cc. of blood were transfused. With the proportions suggested by Lewisohn, it will thus be seen that 2 gm. of sodium citrate are sufficient for the transfusion of 1000 cc. of blood. It is naturally impossible to fix exactly the toxic dose of sodium citrate, but Lewisohn believes that 5 gm. could be safely given, an amount sufficient for the transfusion of 2,500 cc. of blood, which is greatly in excess of what would be/

be required. In this connection it is interesting to note that Robertson,<sup>26</sup> regularly injected 6 gm. of sodium citrate in cases of shock and haemorrhage, and has never observed any harmful effects from this quantity, whether injected with 500 or 800 cc. of blood. The solution which he regularly employs is isotonic, consisting of 160 cc. of a 3.8% solution of sodium citrate.

Sabatini and Hédon<sup>25</sup> have investigated the toxic action of sodium citrate when injected intravenously. According to the latter observer, intravenous injection of a toxic dose determines violent convulsions, tetany, paralysis, salivation, with other signs of violent irritation of the central nervous system. With a fatal dose, death results with violent tetanic spasms, and arrest of respiration - but in nonfatal cases the symptoms disappear rapidly without leaving any results. Hédon found that a toxic dose was better tolerated if injected slowly.

Salant and Wise believe that the toxicity of sodium citrate depends upon the rate of its oxidation in the body; being more toxic for animals in which large quantities are eliminated unchanged.

Hédon, experimenting on rabbits, found that the toxic phenomena associated with an overdose of citrate of sodium could be prevented by the simultaneous injection of a certain amount of calcium chloride solution./

solution. Thus a rabbit of 2.45 kilograms received with impunity an intravenous injection of 50 cc. of 4% solution of sodium citrate (2 gm.) to which calcium chloride had been added in the proportion of .8%, without presenting any toxic symptoms. It was similarly found that the toxic symptoms could be allayed by the immediate injection of calcium chloride solution. These observations suggest therefore that when a moderate amount of citrate of sodium is used for mixing with blood, most of the citrate will already be employed in fixing the calcium ions, and any slight excess will be without toxic effect upon the recipient. A great excess of sodium citrate is therefore inadvisable, although a small excess is probably desirable as erring on the safe side. Hédon suggests that sodium citrate should be mixed with blood in the proportion of .3%, which is slightly in excess of that advocated by Lewisohn.

Even after severe haemorrhage, there is always a considerable amount of blood left in the vessels, and this will still be able to coagulate after transfusion with citrated blood, because the calcium salts remaining in the blood, and of the tissues, are amply sufficient to re-establish the conditions for coagulation in the transfused blood. In order to render the blood incoagulable in vivo, the reserve of calcium in the tissues is such that it would be necessary/



necessary to inject a quantity of sodium citrate greater than the toxic dose. Contrary to expectation, the immediate effects of transfusion with citrated blood is to shorten rather than to prolong the coagulation time. This observation was originally made by Weil, and was confirmed by Lewisohn. A remarkable acceleration of the coagulation time was observed by Lewisohn in a dog which was reinfused with 300 cc. of its own blood, mixed with citrate in the proportion of .2%. Before transfusion, the coagulation time was 5 minutes; but when tested three and six minutes after transfusion, the coagulation time was only ten seconds. The marked hastening of the coagulation of the blood recorded in this experiment was not confirmed in his clinical cases, but in the latter, the tests were made a few hours, or the day after the transfusion. Lewisohn however established the important fact that there was no marked retardation of coagulation after transfusion, the occurrence of which would have limited the general application of the method.

Although no harmful effects have been observed in patients who have been transfused with citrated blood, it has been noted that a chill is more frequent when this method is used than after transfusion with unmodified blood. Bernheim, who has had a large experience with both citrated and unmodified blood, stated/



stated that a chill occurred in from twenty to thirty minutes after the blood had been introduced in about 22% of sodium citrate cases. During this reaction, the temperature may rise abruptly as high as  $104^{\circ}$  -  $105^{\circ}$  F., but the whole disturbance is over in three or four hours, and the patient shows little or no ill effects from it. The chill occurs in spite of the most perfect preliminary tests, but he has never noticed the slightest harmful effect from it on the future course of the illness, or the progress of the patient. Lewisohn recorded 130 cases in which 15% exhibited a chill following the operation. Robertson, employing a much larger amount of sodium citrate, also found that the patient not uncommonly suffered from chill either during, or immediately after, the transfusion; but any discomfort the patient suffered was only temporary.

Transfusion with citrated blood is certainly simpler than any other method, and has the additional advantage that the patient need not come in contact with the donor. It has also made it possible for the blood to be transported, although the necessity for this cannot often arise. Cases have been successfully transfused with citrated blood several hours after its preparation. Citrated blood may remain apparently unaltered for several days. Rous and Turner/

Turner found that haemolysis was well marked after little more than a week. Even although haemolysis may not be present for some days, blood preserved in citrate solution for any length of time should not be used for transfusion, as there is reason to believe that the corpuscles undergo deterioration.

The theoretical objection to Citrate of Sodium as an anticoagulant for transfusion, on the ground that it lowers the blood pressure, is not borne out in practice.

As already mentioned, the question of the preservation of the red blood corpuscles was investigated by Rous and Turner. A simple and practical method of keeping the corpuscles is in citrated whole blood to which sugar solution is added. Human red blood corpuscles can be kept intact when the mixture, consisting of three parts of blood, two parts of isotonic citrate solution (3.8%), and five parts of isotonic dextrose solution (5.4%), is kept in an ice chest. Robertson employed quantities of 250 and 500 cc, of blood preserved in this way, for treatment of urgent cases when there was no time to select suitable donors. Prior to being used, the supernatant fluid was syphoned off, and the original volume of the blood was restored by the addition of a 2.5% solution of gelatine in normal saline. The blood used for transfusion had been kept for periods up to twenty-one/



one days, and in some cases up to 750 cc. of blood were given; but in every case the total amount of the transfusion was made up to 1,000 cc. The effects of the transfusions with preserved blood were as striking as those obtained after transfusion with fresh blood, and the subsequent progress of the patients was equally satisfactory. In certain cases there was a rise in the haemoglobin of from 5% - 20%, which was maintained during the subsequent days. No evidence of increased blood destruction after transfusion was observed, and the improvement in the cases transfused with blood kept for three weeks was as marked as that in cases who received blood kept for shorter periods. It will be noted that in this form of transfusion the red corpuscles are injected without the original plasma. Turner observed that the red blood corpuscles became spherical if preserved in this manner; but that they regained their shape after transfusion, and proved as effective as fresh corpuscles.

EXPERIMENTAL OBSERVATIONS ON THE TRANSFUSION OF BLOOD.

My interest in transfusion of blood was first aroused in 1913 by the frequent reports published in the American journals at that time. It was apparent from the favourable results which were being obtained by different observers that considerable progress had been made in the practice of transfusion, and that it was desirable to be prepared to perform the operation in a satisfactory manner. As at this time the operation of direct transfusion was being practised on the lines suggested by Crile, I thought it advisable in the first place to make myself familiar with the technique of blood vessel surgery by experiments on animals.

It is obvious that for operations on the blood vessels, or for the arterio-venous anastomosis which is necessary for performing direct transfusion, special instruments, materials, and methods of operating are required, if the risk of premature clotting is to be avoided. My object in the first instance therefore was to establish experimentally a reliable technique for the anastomosis and suture of blood vessels. Most of the experiments were made either on the aorta of the cat or the dog's carotid, and both vessels proved suitable for the purpose, although the small size of the former renders the manipulation specially difficult, and demands the greatest



greatest accuracy in operating. The experiments were chiefly directed towards the study of the different methods of vascular suture, and included the repair of longitudinal and irregular wounds of arteries, end-to-end suture of completely divided arteries, arterio-venous anastomosis, and the narrowing and partial occlusion of arteries by suture and by aluminium bands. As certain of these experiments have no bearing upon the subject of transfusion, reference will be made only to the facts which were observed regarding the general principles of technique as illustrated particularly by direct end-to-end anastomosis of blood vessels by suture.

The methods described by Carrel and Guthrie were employed in the first instance, and various modifications were tried in order to find out whether the methods could be improved or simplified to any extent. In anticipation of the conclusions which were come to, it may be stated that no essential modification of the standard Carrel technique was found to be justified. The results of the transverse division and end-to-end suture of the common carotid artery of the dog were particularly successful, and subsequent occlusion of the artery occurred only in one case, in which there was sepsis in the wound, out of a series of ten experiments in which the/

the methods finally adopted were employed. Similar experiments were performed on the aorta of the cat, which was divided and sutured both above and below the inferior mesenteric artery. In spite of the difficulties due to the small size of the vessel, the artery remained perfectly patent in nine out of twelve animals. Failure of such an operation is readily recognised, as ligation or rapid occlusion of the cat's aorta is followed by paralysis of the hind limbs. This occurred only in one of the three cases in which the artery did not remain patent, and in this case apparently a thrombus had formed within a few minutes of the completion of the operation. In the remaining two cases the animals were kept under observation for long periods and it was therefore obvious that the occlusion which resulted from the division and suture of the aorta must have been gradual, and sufficiently delayed to permit the collateral circulation to become established.

The only special instruments which were found necessary, in addition to the needles and materials for suture, were a pair of fine scissors, two light clamps, and a pair of fine blunt-pointed dissecting forceps.

Clamps./

Clamps. Different forms of clamps were tried, including bull-dog forceps, Crile's arterial clamp, and the use of tapes. The most satisfactory instrument proved to be a light Doyen's clamp, which was subsequently used in all the operations for direct transfusions in my clinical cases. With this clamp the right amount of pressure can be easily applied, and the long handles are convenient for holding the vessels in position.

Needles. Fine round needles are required, and none of the ordinary varieties kept in stock by the instrument maker are adapted for the purpose. . The finest cambric needles, No.16, supplied by Kirby, Beard & Co. were found most suitable. Curved needles were not convenient, and the straight variety was always used after the first experiments. These straight needles are flexible to a certain extent, and there is less difficulty in handling them than in the case of curved needles. It is important that the surfaces of the needles should be highly polished, and, as they tend to rust easily, they should only be used once.

Suture materials. Silk was employed in all the experiments, and proved entirely satisfactory. There is a great difference in the quality of the samples of silk sold/

sold for surgical purposes, and only the best quality with long smooth fibres is suitable for suturing blood vessels. The silk which I used is known as "bead silk", and was supplied by James Piersoll & Co. Such threads consist of three twisted strands, each of which is composed of two smaller strands. Six sutures therefore, each consisting of a single strand, were obtained from one thread, and these require to be tested as regards their strength. Certain strands are rough, and should be discarded, and the strength of the strands must be uniform, as the snapping of a stitch during the process of suturing endangers the prospects of perfect coaptation.

It is important to have the silk lubricated with vaseline. This point was investigated, and the risks of thrombosis were found to be greater when the silk was not oiled. The simplest method of preparing the stitch is to draw it through the fingers, previously smeared with vaseline, and this should be done after the needle has been threaded and sterilised.

After experimenting with various needles, clamps, and methods of suturing, the following technique for the end-to-end anastomosis of vessels was adopted.



# I. Preparation of the vessels for suturing.

The operations were performed with aseptic precautions, as it was desired to keep the animals alive. The aorta or the common carotid was exposed for a sufficient distance to permit of the vessel being doubly clamped. A thin sheet of dark dental rubber was then drawn beneath the vessel, in order to protect the sutures, and to offer a contrast to the white silk threads, which were so fine that considerable eye strain was entailed without the use of a background. The artery was then cut across with a pair of scissors midway between the clamps. The divided ends retract, but the adventitial coat hangs like a fringe over the open ends of the vessel, and must be pulled down and cut off short, as otherwise the stitching will be interfered with. Carrel and Guthrie pointed out that thrombosis and occlusion are almost certain to follow if the adventitia is entangled in the line of the suture. A trace of blood is always present within the lumen, even when the vessel has been stripped with the fingers before the clamps are applied, and it is advisable to remove the blood without delay, in case any fibrin is formed. The ends of the vessel should be washed out first with saline, and then with liquid paraffin. During all the steps of the operation, - great care is/

is necessary to avoid rough handling, or injury of the intima by excessive pressure with the clamps. It was found that if the intima were damaged by rubbing or allowed to dry, that thrombosis was almost certain to follow, in spite of the most exact suturing.

## II. Method of suturing.

Carrel and Guthrie recommended the introduction of three guiding sutures, to ensure correct apposition of the ends of the vessels. I found Carrel's method satisfactory, but the number of stay sutures is apt to complicate the operation in the case of small vessels such as the aorta of the cat, and also of medium size arteries such as the dog's carotid. Unless the guiding sutures are kept taut they readily become entangled. Equally good results in my hands were obtained by the use of two guiding sutures, and the method I adopted was as follows.- Two separate sutures were inserted through the entire thickness of the coat of the artery, one in front and one behind, care being taken that the needle passed through corresponding points close to the edge of the open ends of the artery, so that the knot would be outside. The posterior suture was then tied, one end being clamped with the forceps, and the other left/

left long and attached to the needle, to be used for the continuous suturing of the ends of the vessel. The anterior stay suture was not tied till later, and was used as a guide and tractor. The ends of the vessel were then rotated so that the posterior suture was to the right, and the anterior suture to the left, and the anterior edges of the artery were then sutured from right to left. By gentle traction on the guiding sutures, the edges of the artery were kept exactly opposed to each other. When one half of the circumference had been stitched the anterior guiding suture was tied, and the vessel rotated in the opposite direction so that with the same continuous stitch the remaining half of the circumference was also sutured. I found that there was less chance of leakage if a single continuous suture was employed, and that it was better to tie the second guiding suture separately. The individual stitches should be placed as close together, and as near to the cut edge as is practicable, with the certainty of including the whole thickness of the arterial wall. The needle was passed always at right angles to the coat of the artery, so that the minimum of thread was left exposed within the lumen. With the above technique my results showed that in a large proportion of cases the lumen of the vessel remained permanently/

permanently patent. The intima soon completely covers the sutured line, and there is no subsequent bulging or weakness where the artery has been stitched. In two of my cases in which both the common carotid arteries were divided and sutured, casts of the vessels taken several weeks later showed the entire absence of stenosis, and perfect reconstruction of the lumen. The other specimens which are illustrated confirm these observations. While the division and suture of an artery in the absence of the thrombosis causes no apparent alteration in the intima, the wide separation of the artery from its sheath, which is necessary for performing the operation, causes considerable thickening of the outer coats, and occasionally some loss of elasticity in the vessel wall.

#### Arterio-venous anastomosis.

In one case an anastomosis was made between the common carotid and the external jugular vein. Both vessels were divided, and the proximal end of the common carotid was united to the peripheral end of the vein. The same technique was found satisfactory, the only modification necessary being due to the greater size of the lumen of the vein. By placing the sutures close together in the artery, and slightly wider/

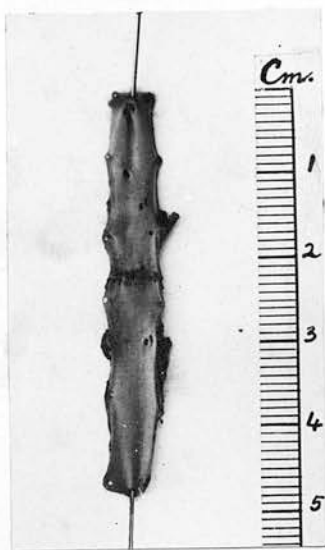


wider apart through the wall of the vein, the junction was satisfactorily completed, but the certainty of a permanently successful result was naturally less than when vessels of similar calibre were united. The junction in this case remained patent for three weeks, during which time a thrill was easily felt in the neck. When the animal was killed one month after the operation, the junction was found occluded by a small white thrombus.

My experiments on blood vessels showed that arteries could be incised or completely divided and restored by suture with little risk of clotting. At the same time it was clear that the operation was sufficiently difficult to make it impracticable as a routine method for the direct transfusion of blood in clinical cases. The difficulty of end-to-end suture of a small artery like the radial, which is comparable in size to a cat's aorta, would be much greater in the case of direct transfusion of blood than in an animal experiment, because of the greater diameter of the vein to which the artery would have to be united. Apart from the technical difficulties of end-to-end suture between vessels of different size, the close proximity of the patients' arms, which is necessary for direct transfusion, is bound to limit the access; and, as it may be difficult to keep/

keep such cases perfectly still, it would sometimes be impossible to perform the operation satisfactorily. Although the same objections do not apply to Crile's method of transfusion by means of a canula which unites the intima of the two vessels, still with this method close apposition of the patients' arms is necessary, and, while the anastomosis is perfect and the risk of clotting is reduced to a minimum, it is bound to be difficult sometimes to make sure that the vessels are not kinked or stretched, which can only be done by palpation of the vein.

The next object of my experiments therefore was to find out whether direct transfusion could not equally well be done by some means which left more space between the patients' arms than is afforded by suture or by Crile's Canula. It was hoped also to form an opinion from the experiments of the value of transfusion in cases of haemorrhage, and to compare the value of saline with transfusion in the treatment of such cases.



a



b



c



d

Fig. 1. Transverse division and Circular Suture of Cat's aorta.  
 A. 48 hours after operation. Lumen patent.  
 B. Cat 4 hours after operation. Lumen patent.  
 C. Thrombus at sutured line.  
 D. Cat showing paralysis of hind quarters due to thrombosis and occlusion of lumen.

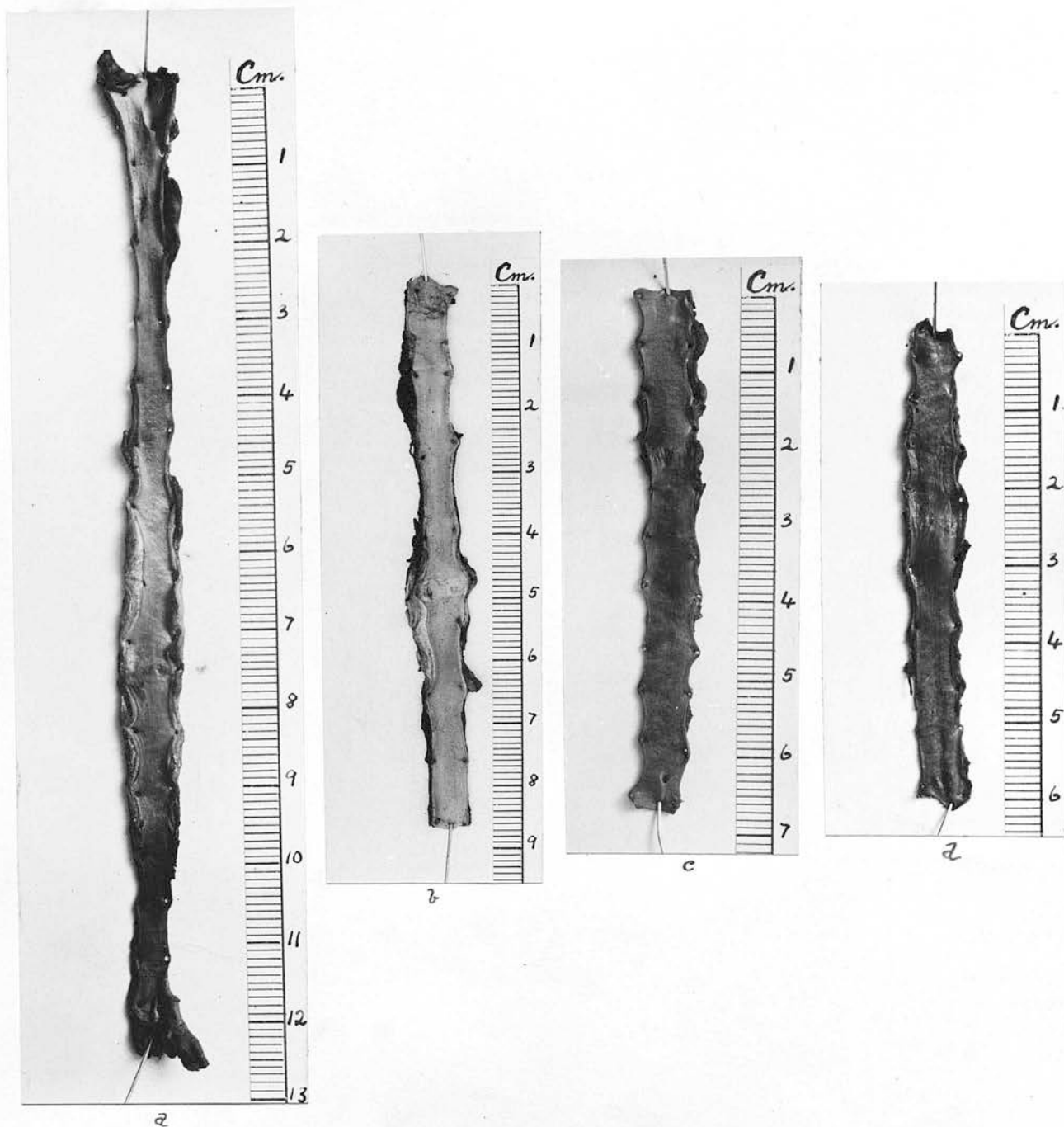


Fig. 2. Transverse division and circular suture of dog's carotid.  
 A. Three weeks after operation.  
 B. Six " " "  
 C. Seven " " "  
 D. Eight " " "

The writer's modification of Carrel's technique was employed. The specimens show complete reconstruction of the lumen and the sutured line covered over by intima.



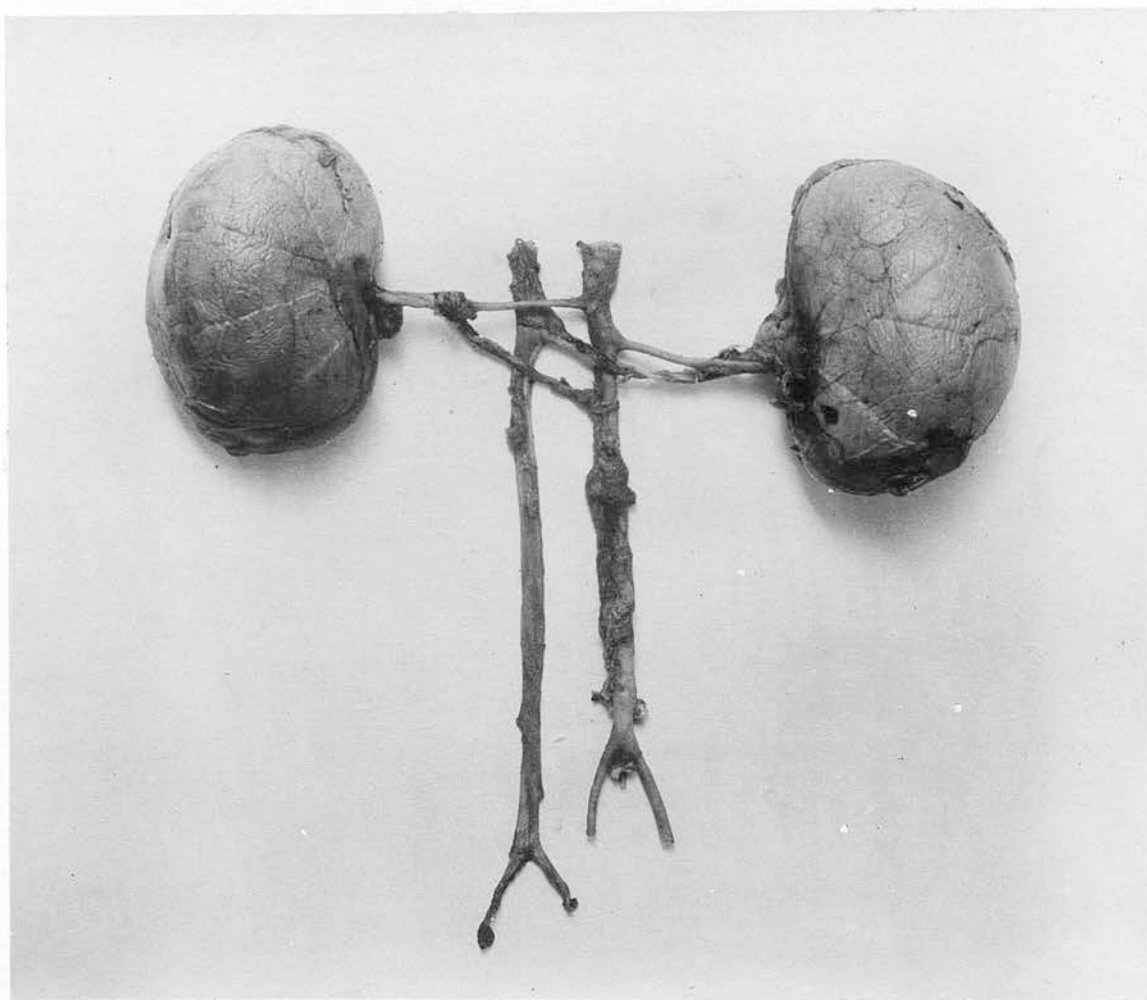


Fig. 3. Cat's aorta  $3\frac{1}{2}$  weeks after transverse division and suture. Lumen patent. Shows thickening around the portion of vessel separated for performance of the anastomosis.

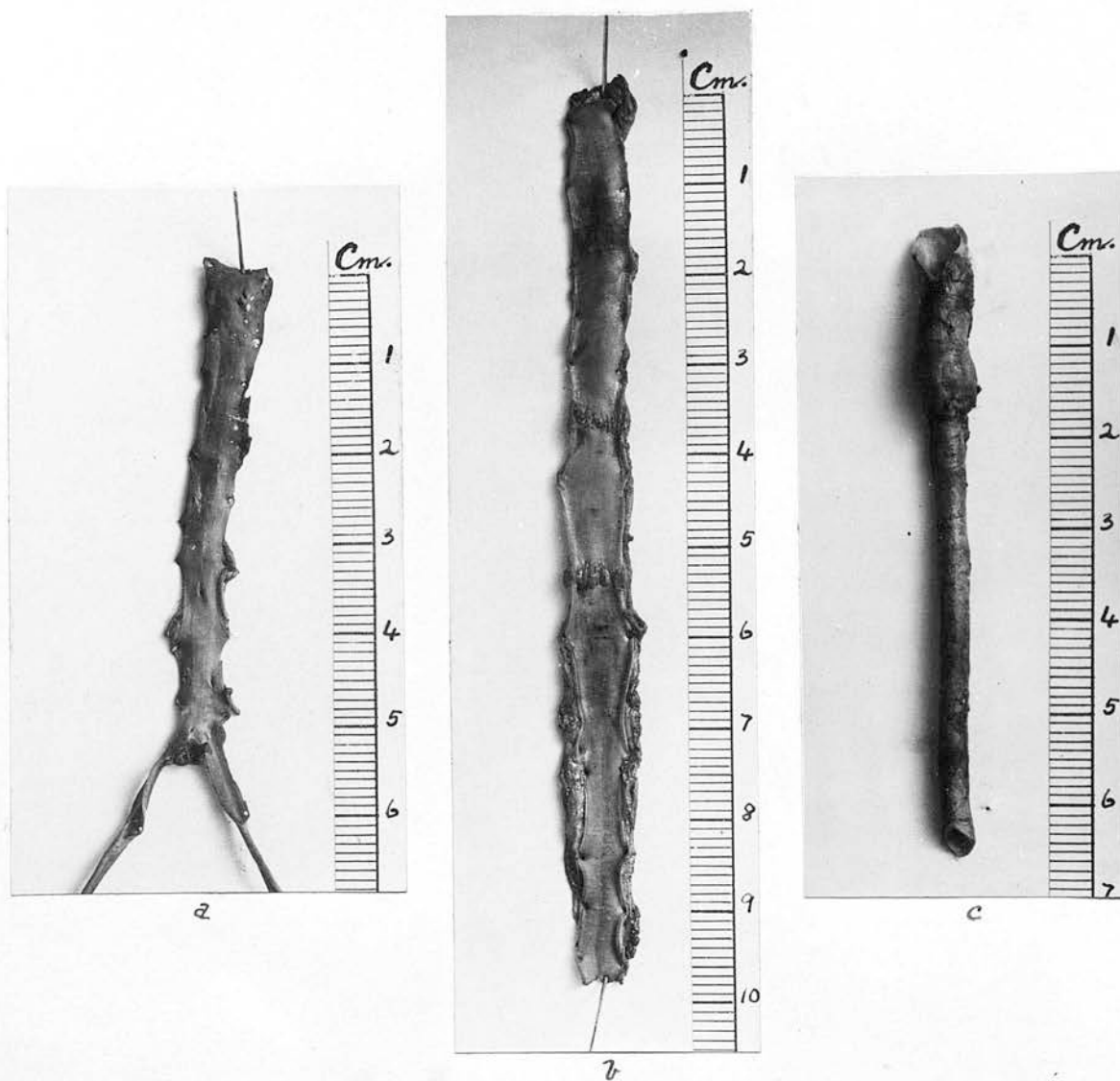


Fig. 4. Specimens illustrating the results of vascular suture.

- A. Longitudinal incision,  $\frac{3}{4}$  inch in length, of cat's aorta, 6½ weeks after suture.
- B. Removal and immediate suture of a segment of dog's carotid. Artery patent 2½ weeks later.
- C. Arterio-venous anastomosis between the carotid and external jugular of the dog. The junction was patent for 3 weeks.

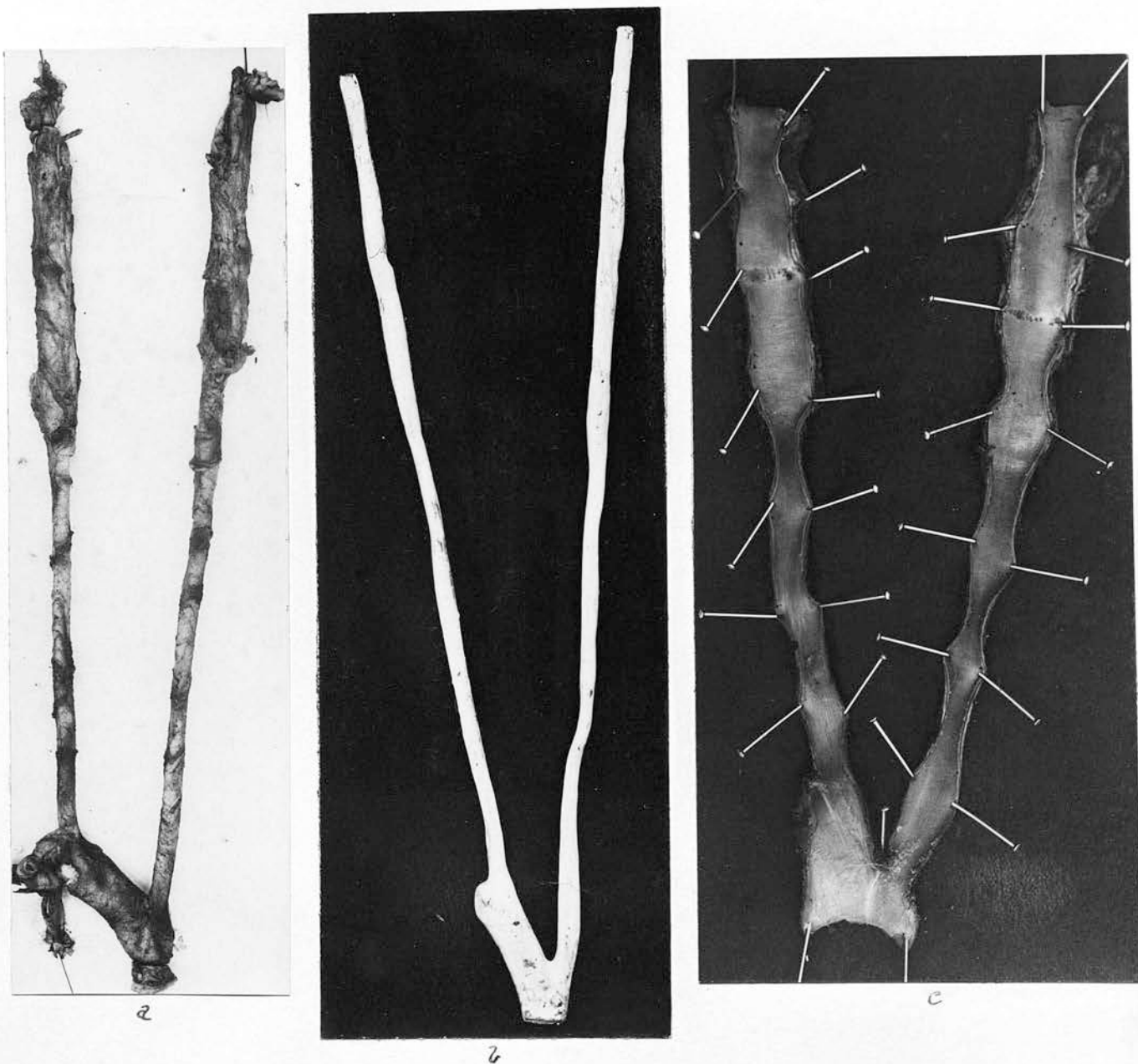


Fig. 5. Transverse division and circular suture of both carotid arteries. (Dog's) 4 weeks after operation.

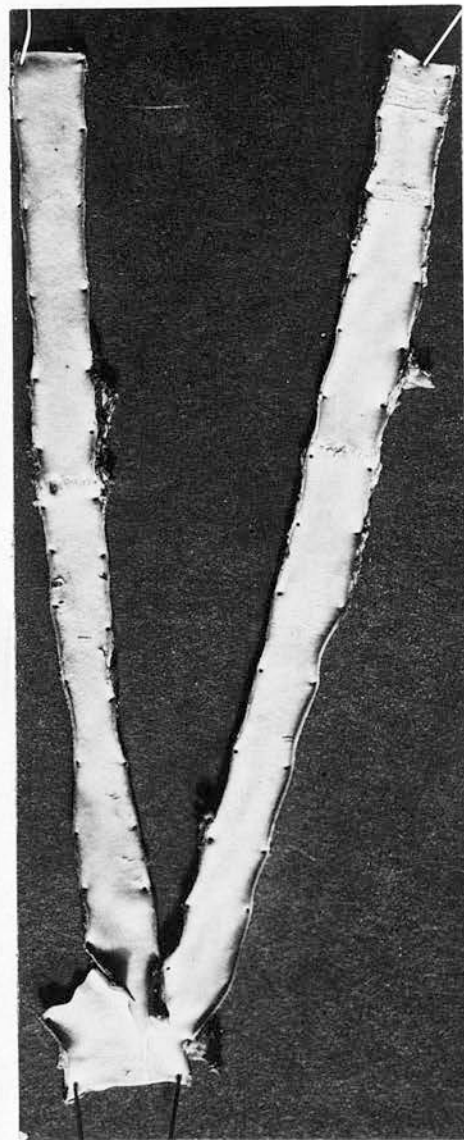
- A. Shows thickening of portions of vessels detached from the surrounding parts.
- B. Wax cast showing the patency of the vessels.
- C. Shows the repair of the sutured line in both carotids.



a



b



c

Fig. 6. Transverse division and circular suture of both carotid arteries (Dog's) 4½ weeks after operation.

- A. Shows thickening of adventitial coat of arteries due to stripping from the sheath.
- B. Cast showing absence of stenosis. The reverse side of the cast is shown because of a minute localised projection at the sutured line on one side.
- C. Vessels opened to show the repair after end to end suture.



Observations on the technique of Transfusion.

As it seemed desirable, for the reasons stated above, to leave a certain space between the arms of the donor and recipient during transfusion, it was decided to employ some form of tube as a connection between the vessels. For simple transfusion experiments large vessels, like the femoral or carotid, and the corresponding veins are generally used. Many experiments in the past have shown that it is possible to transfuse a large amount of blood without clotting through a tube which has not been prepared in any special way, or has simply been washed out with carbonate of soda or sodium citrate solution. Only a few minutes are necessary completely to re-animate an exsanguinated dog by transfusion, and the absence of clotting is due to the short duration of the transfusion, and to the fact that it is possible to use a large tube in proportion to the size of the artery. The conditions are quite different when the blood is transfused from the human radial artery as the diameter of the artery is small; and the volume of blood passing through the canula in a given time must be much less than from the dog's carotid. In cases where the radial artery is small, transfusion may need to be continued for half an hour or more. It was decided therefore to use canulae similar in size to those suitable for the human radial artery, and these were employed after a preliminary coating with paraffin.

Preparation of canulae.

Glass canulae,  $2\frac{3}{4}$  inches in length, were used, with an external diameter of 2 - 3 mm., the walls being as thin as was consistent with strength. In making the canulae, slight bulbous thickenings were blown at either end, so that they could be more securely tied into the vessels. The canulae were sterilised in the autoclave, and then dipped into the paraffin mixture, which had previously been sterilised and liquefied. It was found that the best way to coat the glass tubes was to lift them out of the dish of paraffin with forceps, and, after allowing the excess of paraffin to run out, to wipe the lower end of the canula with a piece of sterile gauze while it was being held vertically. If this precaution is not taken there is a tendency for the paraffin to harden too quickly, and thus block the ends of the tubes. When the tubes are satisfactorily coated the paraffin forms a thin greyish film on cooling.

It was decided to coat the tubes described above as the result of the following experiments; in which hard paraffin was compared with liquid paraffin.

Dog/

Dog, 8.25 kilos.

Morphia acetate, gr.  $\frac{1}{2}$ , half an hour before operation.  
Anaesthesia induced with chloroform, and maintained with ether.

A. Object:- To test the relative efficiency of liquid and solid paraffin as lubricants of canulae introduced into the circulation.

Method:- Both femoral arteries were exposed, and clamped in two places. An incision was made just proximal to the peripheral clamp, and the artery washed out with saline and liquid paraffin. Two canulae, of equal external and internal (3 mm.) diameter were then introduced in a proximal direction, one lubricated with liquid paraffin, and the inner surface of the other coated with a mixture of

Hard paraffin ..... 2 parts.

Soft paraffin ..... 2 parts.

Stearin .... 1 part.

The canulae were then slid into the peripheral part of the artery and tied in position. In each limb, the peripheral clamp was first removed, then the proximal clamp, and the circulation was re-established through the canulae.

Results/

Results:- (a) Flow started, 11.2 a.m.

(b) Pulse becoming weaker in the limb with the liquid paraffin canula, 11.29 a.m.

(c) Before removing both canulae at 12 noon, the pulse was very feeble beyond the liquid-lubricated canula, but strong beyond the other. On removal, a large filiform clot was found in the whole length of the liquid-lined canula; but only a very small flaky clot in the other. The clots in both cases were adhering to the tubes.

Conclusion:- Solid paraffin is the better lubricant.

B. Object:- To find if a film of hard paraffin in a receiving dish delays clotting.

Method:- A porcelain dish was coated with the same mixture of paraffin, etc., as in the first experiment, and 25 cc. of blood were withdrawn into it from the right external jugular.

Result:- The blood clotted in 14 minutes. Clotting occurred in four minutes in a control dish.

Conclusion:- A lining of hard paraffin to the receiving dish delays clotting.



First Transfusion Experiment.

Nov. 5th, 1913.

Donor:- Airedale.

Recipient:- Fox Terrier.

Preliminary hypodermic injection of morphia, gr.  $\frac{1}{4}$ .

Anaesthesia induced with chloroform and maintained with ether.

Stages of operation:- The animals were placed close together, lying head to tail, so that the necks were approximated.

The operation was done with aseptic precautions, as it was desired to keep both animals alive.

Donor:- The right common carotid artery was exposed through a mid-line incision. A short length of the vessel was dissected free, and two light blood-vessel clamps were applied about 1 inch apart. A V-shaped incision was then made in the part of the artery between the clamps, and all trace of blood was washed out with a pipette of saline. The intima was lubricated with a pipette of liquid paraffin, and a paraffined glass canula was tied into the proximal end of the artery.

Recipient:- The left external jugular vein and the left femoral artery were exposed by suitable incisions. The external jugular//

jugular vein was ligatured high up, clamped immediately below, and cut across below the ligature. The lumen was then treated in the same way as the carotid artery of the donor. The preliminary steps for transfusion having been completed, the left femoral artery was opened, and was then allowed to bleed till the blood had practically ceased to flow, and the respirations were reduced to a few convulsive movements. The femoral artery was then ligatured, and transfusion was commenced one minute after apparent death. The recipient quickly responded to the transfusion, which lasted  $3\frac{1}{2}$  minutes, by which time the pulse and circulation had completely recovered. The operation was completed by ligation of the external jugular vein, and closure of the wounds. The whole experiment lasted one hour, and both animals were out of the anaesthetic fifteen minutes later.

Accurate weights of the animals were not recorded, but the donor was a much larger dog and able to suffer a considerable loss of blood. Although its blood pressure was much reduced at the time, in ten days the dog had completely recovered from the anaemia. Both animals recovered, and their wounds healed by first intention.

Comment:-/

Comment:- The experiment showed that.-

- (a) A dog bled to the point of death can be re-animated and restored to complete health by transfusion of blood from another dog.
- (b) The transplanted blood retains its physiological functions.
- (c) An animal bled to a moderate degree can quickly recover the loss of blood.
- (d) The method adopted can be performed aseptically.

Second Transfusion Experiment:-

Nov. 20th, 1913.

Donor:- Male Scotch Terrier,  $13\frac{1}{2}$  kilos.

Recipient:- Mongrel, 7.2 kilos.

Preliminary hypodermic injection of morphia, gr.  $\frac{1}{4}$ .

Anaesthesia induced with chloroform and maintained with ether.

Stages of operation:- The preliminary stages were similar to those of experiment 1, but in addition a canula was tied into the femoral artery, and connected to a manometer so that changes in the blood pressure could be noted.

Observations on the effects of bleeding and transfusion on the blood pressure:-

A continuous blood pressure tracing was taken during the operation, but as the animal was bled from the canula in the left femoral artery, the tracing was interrupted each time this was done. Exact observations however were made on.-

- (a) the effects of the successive bleedings,
- (b) the effects of transfusion.

Calculating/



Calculating the total volume of the blood as being equal to one-thirteenth of the body weight, approximately one half of the circulating blood was withdrawn from the circulation. The blood pressure fell from 151 mm. to 41 mm. of mercury, when the pulse was barely perceptible, and the flow of blood was much reduced in volume and rate, and the animal was in extremis. After each successive withdrawal of blood, it was noted that the blood pressure fell, but tended to rise again slightly. The extremely low blood pressure after bleeding was due partly to the rapidity with which the blood was lost. The immediate effect of transfusion was to raise the blood pressure in one minute from 41 mm. to 151 mm. of mercury, the normal figure. Transfusion was continued for two minutes and the blood pressure was finally increased by over-transfusion to 192 mm. of mercury. The following figures illustrate the above point

Blood pressure :

Before bleeding	151 mm. of mercury.
After bleeding 100 cc.	114.
150 cc.	105.
210 cc.	84.
250 cc.	52.
Continued fall to	41.

Blood/

Blood pressure immediately before transfusion	41 mm.
One minute after transfusion . . . . .	151 mm.
Three minutes after transfusion . . . . .	192 mm.

The effects of bleeding on the circulation as shown by the fall in blood pressure was further demonstrated by the diminution in the volume of the pulse, and by the fact that at the end of the operation the time taken to withdraw a given amount of blood was double that at the commencement. With intervals, the duration of the transfusion was twenty minutes, and the canula was still patent at the close; Although no exact estimation could be made of the amount of blood lost by the donor, there is no doubt that it was considerable, and the animal was markedly anaemic. As the pulse was somewhat feeble, 200 cc. of saline were given intravenously, after which the blood pressure was observed to be increased, and the general condition improved. At the conclusion of the experiment the wounds were sutured, and there was primary healing in both cases. The donee did not show any ill effects from the overtransfusion which it had received, and it remained perfectly well after coming out of the anaesthetic. The donor also made an excellent recovery, but returned more slowly to the normal condition.

Comments:-/

Comments:- Transfusion was in this case successful in reanimating an animal which had lost approximately half its volume of blood and whose blood pressure had been reduced to a minimum. Infusion of saline, in the case of an animal suffering from a slighter degree of exsanguination, led to an increase in blood pressure, and improved general condition, but recovery was more gradual than in the case of the other animal, which had been bled to a much greater extent, but was treated by transfusion of blood.

### Third Transfusion Experiment.

Nov. 27th, 1913.

Observations on the effect of normal saline (Locke's solution) on blood pressure after bleeding.

Airedale, 10.350kilos.

Anaesthesia induced with chloroform and maintained with ether.

Preliminary hypodermic injection of morphia, gr  $\frac{1}{4}$ .

Stages of operation:- Both femoral arteries and the right external jugular vein were exposed. The blood pressure was taken from the left femoral artery. Blood was withdrawn from the right femoral artery. The left external jugular vein was ligated/

ligated distally, and controlled by a clamp proximally. Between these points the vein was opened and washed out with normal saline.

The experiment was designed to observe the effect of replacing blood withdrawn from an animal by an equivalent amount of Locke's solution.

At the commencement of the experiment the blood pressure was 120 mm. of mercury. This pressure was maintained at a steady level, till the animal was bled, when the pressure rapidly fell. After losing 240 cc. of blood the pressure was reduced to 75 mm., but gradually rose again to 100 mm. 70 cc. (total 310 cc.) were then withdrawn, and the pressure again fell to 75 mm., but after a brief interval rose gradually to 88. 310 cc. of Locke's solution were now infused, and the blood pressure returned to the normal level - 120 mm. The blood pressure being now the same as at the beginning of the experiment the animal was again bled to the extent of 200 cc., as a result of which the blood pressure fell to 90 mm., but gradually rose again to 107 mm. The normal volume of the blood was again restored by an infusion of 200 cc. of saline, following which the blood pressure reached the level of 118 mm., at which level it remained. The removal of 60 cc. of blood now caused a fall to 90 mm., with a gradual subsequent rise to 103 mm. Infusion of 60 cc. of saline did not cause any/



any immediate rise of the blood pressure, but this again increased to 118 mm. After an interval of eight minutes the temporary rise of blood pressure was followed by a fall to 100 mm. 60 cc. of blood were again taken off, and the pressure fell to 80 mm. Infusion of 60 cc. of saline caused a rise to 90 mm, increasing gradually to 100 mm., which fell suddenly to 74 mm. At this stage the animal was very feeble, and owing to the extreme dilution of the blood was suffering from a lack of corpuscles. A further infusion of 160 cc. of saline failed to increase the blood pressure, which continued to fall till it reached 47 mm. when the animal died.

All the blood withdrawn during this operation was replaced by saline, so that the total volume of fluid in the circulation was approximately the same at the end of the experiment.

### EXPERIMENT III./

EXPERIMENT III.

TIME.		BLOOD PRESSURE,	REMARKS.
Min.	Sec.	mm. of Hg.	
00	00	120	
07	00	120	
to			
08	10	75	Bled 240 cc.
09	10	100	
to			
09	30	75	Bled 70 cc.
17	10	88	
to			
19	30	120	Saline 310 cc.
20	10	120	
to			
20	40	90	Bled 200 cc.
21	50	107	
to			
23	20	118	Saline 200 cc.
29	10	118	
to			
29	40	90	Bled 60 cc.
31	00	103	
to			
31	40	103	Saline 60 cc.
42	00	118	
to			
50	00	100	Trace stopped.
52	20	100	
to			
52	50	80	Bled 60 cc.
53	20	80	
to			
54	20	90	Saline 60 cc.
55	20	74	
to			
56	30	47	Saline 140 cc. Animal died.

Comments:- This experiment showed that a marked fall in blood pressure follows immediately on profuse haemorrhage but that the pressure rapidly increases again, although it does not reach the normal. Infusion of an equivalent amount of saline will restore the blood pressure to the same level as before the haemorrhage. After subsequent haemorrhages, infusion of saline will restore the blood pressure almost to normal, but the return becomes more and more gradual, and a stage is reached at which the pressure progressively falls, in spite of the replacement of the blood by saline. The experiment also shows that while saline will restore the blood pressure sufficiently in cases of moderate haemorrhage, when the haemorrhage is excessive it fails to keep the blood pressure at the level necessary to maintain life; and it altogether fails to provide a substitute for the lost corpuscles.

#### Fourth Transfusion Experiment.

8th Dec. 1913.

Donor:- Scotch bitch, 11.65 kilos.

Recipient:- Male fox terrier, 6.15 kilos.

Preliminary hypodermic injection of morphia, gr.  $\frac{1}{4}$ .

Anaesthesia induced with chloroform, and maintained with ether.

Stages/

Stages of Operation:- The animals were placed head to tail, with their necks close together. The operation was done with aseptic precautions.

Recipient:- The left external jugular vein and the left common carotid were exposed. The carotid artery was used for the blood pressure observations, and the external jugular vein for the subsequent infusion and transfusion. The right femoral artery was exposed for withdrawal of blood.

Donor:- The right common carotid was exposed after the necessary dissection of the recipient's vessels. The details of the operation were the same as those described in experiment I.

The object of the experiment was to compare the effects of infusion of saline and transfusion of blood on the blood pressure, and as means of treatment in cases of excessive haemorrhage.

Observations on blood pressure. (Figure 7.)

(a) After saline.

(b) After transfusion.

The/



The blood pressure of the recipient was 134 mm. at the commencement. After bleeding to the extent of 100 cc. the pressure immediately fell to 67 mm., but gradually rose again to 125 mm. A second bleeding of 60 cc. caused the pressure to fall suddenly to 49 mm., from which level it slowly rose to 62 mm. A third bleeding of 150 cc. reduced the pressure to 49 mm., and at this stage the first infusion of Locke's solution was given; 175 cc., an amount equal to the blood previously lost, were introduced by means of a funnel and tubing, connected to a canula in the external jugular vein of the recipient. This was followed by an immediate but irregular rise in the blood pressure to 126 mm. Fresh bleeding of 100 cc. produced a rapid fall in the pressure to 49 mm., but the infusion of 100 cc. of saline caused a temporary rise to 98 mm., followed by a slow fall to 89 mm. A fresh bleeding of 65 cc. lowered the pressure rapidly to 45 mm. An infusion of 65 cc. of saline caused only a slight rise of pressure to 58 mm., and a further bleeding of 50 cc. still further reduced the pressure to 40 mm. With the pressure at this extremely low level it was found that saline failed to raise the blood pressure (infusion of 50 cc.); The animal was now completely exsanguinated, and the pulse was barely perceptible.

At this stage the transfusion of blood was started, //

started, the canula having been previously fixed in the donor's carotid artery. The connection between the circulation of the two animals was rapidly effected. The first transfusion of blood lasted for  $2\frac{1}{2}$  minutes, and produced an immediate effect on the blood pressure, which rapidly rose to 134 mm. Subsequent to this the animal was again bled to the extent of 50 cc., and there was a rapid fall of pressure to 67 mm. Blood was transfused therefore for a second time for a period of  $2\frac{1}{4}$  minutes, and the pressure again rapidly rose to 112 mm. The rise of pressure in this instance was less than after the first transfusion, and was only temporary, falling rapidly to 54 mm. A third transfusion was therefore carried out for a period of two minutes and this caused the blood pressure to rise rapidly to 112 mm. The final condition of the animal was satisfactory in every respect, and the experiment was therefore concluded with the blood pressure gradually returning to the same level as at the commencement of the operation.

The donor was killed at the conclusion of the experiment. After ligating the vessels, the recipient's wounds were stitched, and the animal made an uninterrupted recovery. The wounds healed by first intention.

EXPERIMENT IV.

TIME.		BLOOD PRESSURE.	REMARKS.
Min.	Sec.	mm. of Hg.	
00	00	134	
00	40	134	
to			Bled 100 cc.
03	50	67	
10	40	125	
to			Bled 60 cc.
11	40	49	
16	20	62	
to			Bled 15 cc.
16	50	49	
17	00	49	
to			Saline 175 cc.
19	00	126	
19	50	126	
to			Bled 100 cc.
20	50	49	
21	20	52	
to			Saline 100 cc.
22	50	98	
34	10	89	
to			Bled 65 cc.
35	20	45	
35	30	45	
to			Saline 65 cc.
36	40	58	
38	00	58	
to			Bled 50 cc.
38	50	40	
38	50	40	
to			Saline 50 cc.
39	30	40	
39	50	40	
to			Blood trans-
42	20	134	fused.

EXPERIMENT IV. (Continued.)

TIME.		BLOOD PRESSURE	REMARKS.
Min.	Sec.	mm. of Hg.	
43	10	134	
to			Bled 50 cc.
43	50	67	
44	00	67	
to			
45	100	112	Blood transfused
to			
45	40	54	
47	40	54	
to			Blood transfused
49	30	112	

Comments:- In this experiment, the effects of saline in restoring the blood pressure after haemorrhage confirm the observations made in experiment III. The extreme fall of blood pressure after each withdrawal of blood was due to the rapidity with which it was lost. After repeated haemorrhages it is apparent that replacement of the blood by an equal amount of saline solution fails to prevent the blood pressure from falling to a dangerous extent.

An animal reduced to a moribund condition after rapid profuse haemorrhages for which saline infusion has failed to compensate can be completely reanimated by transfusion of blood.

It is also evident that alternate withdrawal of blood and transfusion can be carried on almost indefinitely without injurious effects to the animal, and that the transplanted blood retains its function.



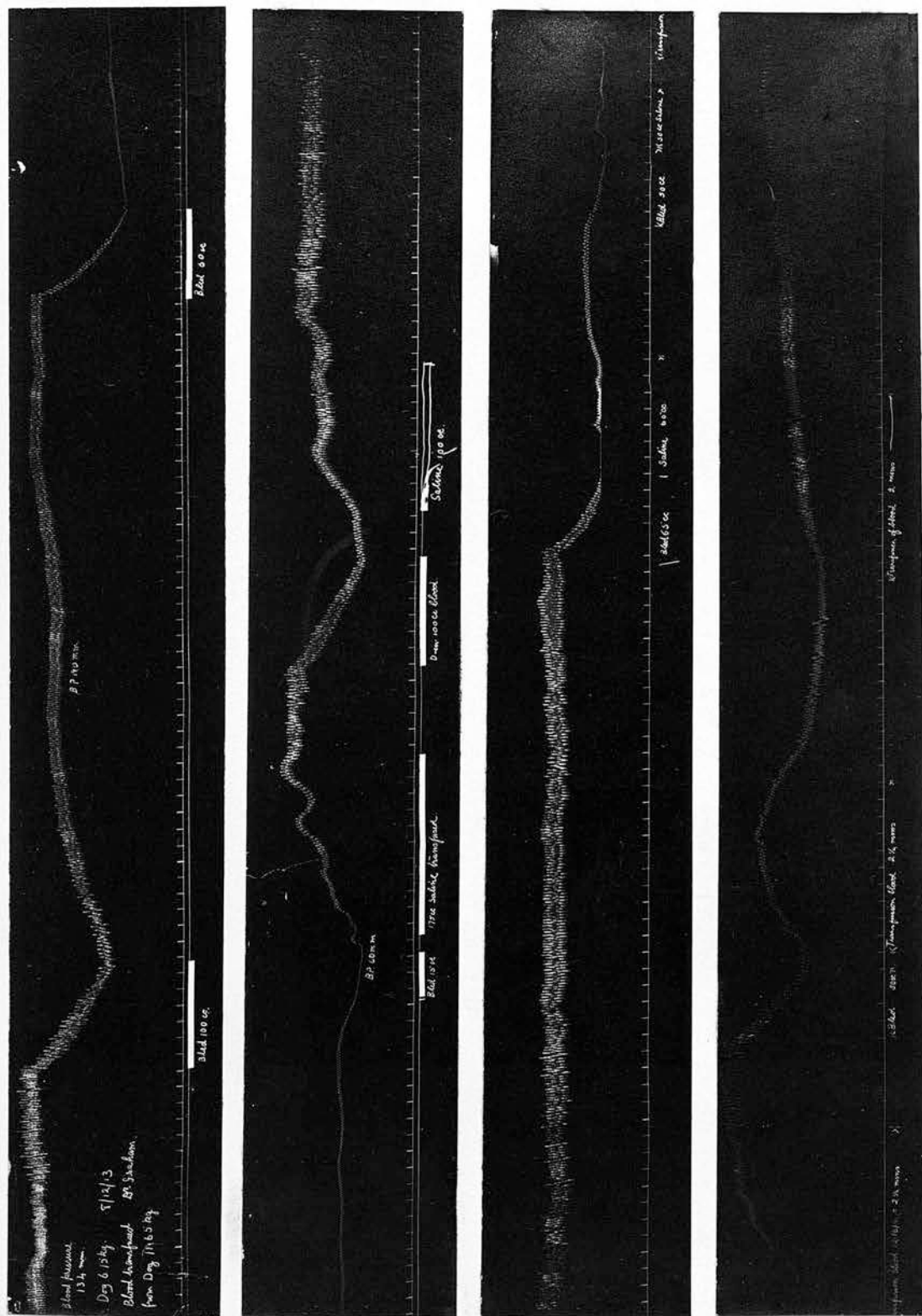


Fig. 7. Experiment IV. Blood pressure tracing showing the effects of bleeding, infusion of saline and transfusion of blood.

Fifth transfusion experiment.

16th Dec. 1913.

Donor:- Collie.

Recipient:- Scotch terrior bitch, 8.25 kilos.

Preliminary injection of morphia, gr.  $\frac{1}{4}$ .

Anaesthesia induced with chloroform and maintained with ether.

Stages of operation:- The animals were placed head to tail and after the preliminary steps of the operation had been completed, they were fixed close together with their necks opposite each other. The operation was done with aseptic precautions.

Recipient:- The left common carotid was exposed, by an incision on the left side of the neck, and was connected to a manometer for blood pressure observations.

The left external jugular was prepared for saline infusions.

The right external jugular vein was exposed through a separate incision on the right side of the neck, and was later connected to the canula of the donor for the reception of blood.

A canula was tied into the left femoral artery for the withdrawal of blood.

Donor:- /

Donor:- The right common carotid artery was exposed by an incision in the neck, and after isolating and lubricating a segment of the artery with saline and liquid paraffin, a paraffined glass transfusion canula was tied into its proximal end.

The experiment was a repetition of the preceding one, and was designed to observe the effects of transfusion of saline (Locke's solution) in comparison with those of blood, in cases of grave haemorrhage.

Observations on blood pressure following haemorrhage, transfusion of saline, and blood transfusion. (Fig.8)

At the commencement of the experiment, the blood pressure taken from the carotid was 140 mm. The animal was bled repeatedly and the blood replaced by an equal amount of Locke's solution, till the blood pressure remained at a dangerously low level. When the stage was reached at which saline failed to produce any increase in the pressure, blood was transfused.

First bleeding:- 100 cc. This was followed by a rapid fall of pressure from 140 mm. to 96 mm., from which point it gradually rose again to 130 mm.

First/

First saline infusion. 100 cc. The pressure rose regularly to 120 mm. of mercury.

Second bleeding. 100 cc. Pressure fell rapidly to 104 mm., but slowly rose again to 112 mm.

Second infusion of saline. The gradual rise of pressure noted after the last bleeding continued without any obvious difference, till it reached 150 mm.

Third bleeding. 100 cc. The pressure immediately fell to 100 mm. and then increased gradually to 110 mm.

Third saline infusion. 100 cc. The rise previously noted after the last bleeding continued in the same proportion till it reached 132 mm, and the pressure was maintained at this level for a considerable time.

Fourth bleeding. 70 cc. This was followed by a gradual fall to 92 mm., at which level the pressure remained constant.

Fourth saline infusion. 70 cc. This produced an abrupt rise of pressure to 126 mm.

Fifth/



Fifth bleeding. 65cc. The pressure fell abruptly to 62 mm.

Fifth and sixth saline infusions. 65cc. This caused a gradual rise to 64 mm., Accordingly an additional 100 cc. of saline were injected, being that amount in excess of blood previously withdrawn. The effect of this additional amount of saline was to raise the pressure from 64 mm. to 118 mm.

Sixth bleeding. 85cc. The pressure fell rather rapidly to 50 mm., a lower level than it had previously reached.

Seventh saline infusion. 85 cc. Following this, the pressure rose very gradually to 90 mm.

Seventh bleeding. 75 cc. The pressure fell gradually to 20 mm. There was a tendency for the blood to clot in the canula in the femoral artery from which the blood was being withdrawn. The animal at this stage was now reduced to an extreme degree of exsanguination.

Eighth saline infusion. 75 cc. This failed to cause much increase of pressure, which rose only to 30 mm.

Eighth bleeding. 35 cc. The animal at this stage was almost moribund, and it took 3 minutes 10 seconds to withdraw the 35 cc. of blood, about one-sixteenth of the volume which would have been delivered in the same time at the commencement of the operation. This gradual withdrawal of a further amount of blood reduced the pressure to 22 mm.

Ninth infusion of saline. 35 cc. This produced a slight rise to 28 mm. As the animal could not be maintained alive much longer, it was decided to try the effects of transfusion.

First transfusion of blood. Three minutes. From the commencement of the transfusion, the blood pressure gradually rose, till it reached 130 mm. at the end of the transfusion in three minutes time. Subsequently the pressure/

pressure was maintained at a level of 110 mm. for several minutes.

Ninth bleeding. 100 cc. This caused practically no change in the pressure, probably because of over-transfusion.

Tenth bleeding. 100 cc. The pressure fell to 90 mm;

Second transfusion. One minute. Following this transfusion of blood, the pressure rose again to

110 mm. Although the pressure in the recipient was not as high as at the commencement of the operation, further transfusion was discontinued, as the donor was in poor condition from the effects of the anaesthetic and loss of blood. The donor was accordingly killed. The recipient animal was in good condition at the end of the operation, and the wounds were stitched after ligating the vessels. The animal made an uninterrupted recovery.

EXPERIMENT V.

TIME.		BLOOD PRESSURE;	REMARKS.
Min.	Sec.	mm. of Hg.	
00	00	140	
01	45	140	
to			Bled 100 cc.
02	20	96	
05	30	130	
to			Saline 100 cc.
06	40	140	
08	00	140	
to			Bled 100 cc.
08	30	104	
10	00	112	
to			Saline 100 cc.
10	35	150	
12	0000	150	
to			Bled 100 cc.
12	30	100	
13	10	110	
to			Saline 100 cc.
14	00	132	
22	50	132	
to			Bled 70 cc.
23	40	92	
24	50	92	
to			Saline 70 cc.
25	20	110	
25	50	126	
to			Bled 65 cc.
26	30	62	
28	00	62	
to			Saline 65 cc.
29	10	64	
30	20	64	
to			Saline 100 cc.
31	20	118	



EXPERIMENT V. (Continued.)

TIME.		BLOOD PRESSURE.	REMARKS.
Min.	Sec.	mm. of Hg.	
32	10	118	
to			
33	10	50	Bled 85 cc.
34	00	50	
to			
35	50	90	Saline 85 cc.
37	20	80	
to			
40	30	20	Bled 75 cc.
50	10	20	
to			
60	20	30	Saline 75 cc.
61	30	30	
to			
64	50	22	Bled 35 cc.
65	40	22	
to			
66	30	28	Saline 35 cc.
67	00	28	
to			
70	10	130	Blood trans- fused.
74	00	110	
to			
74	50	90	Bled 100 cc.
75	40	90	
to			
76	40	90	Bled 100 cc.
76	50	90	
to			
77	50	110	Blood trans- fused.

Comments:-/

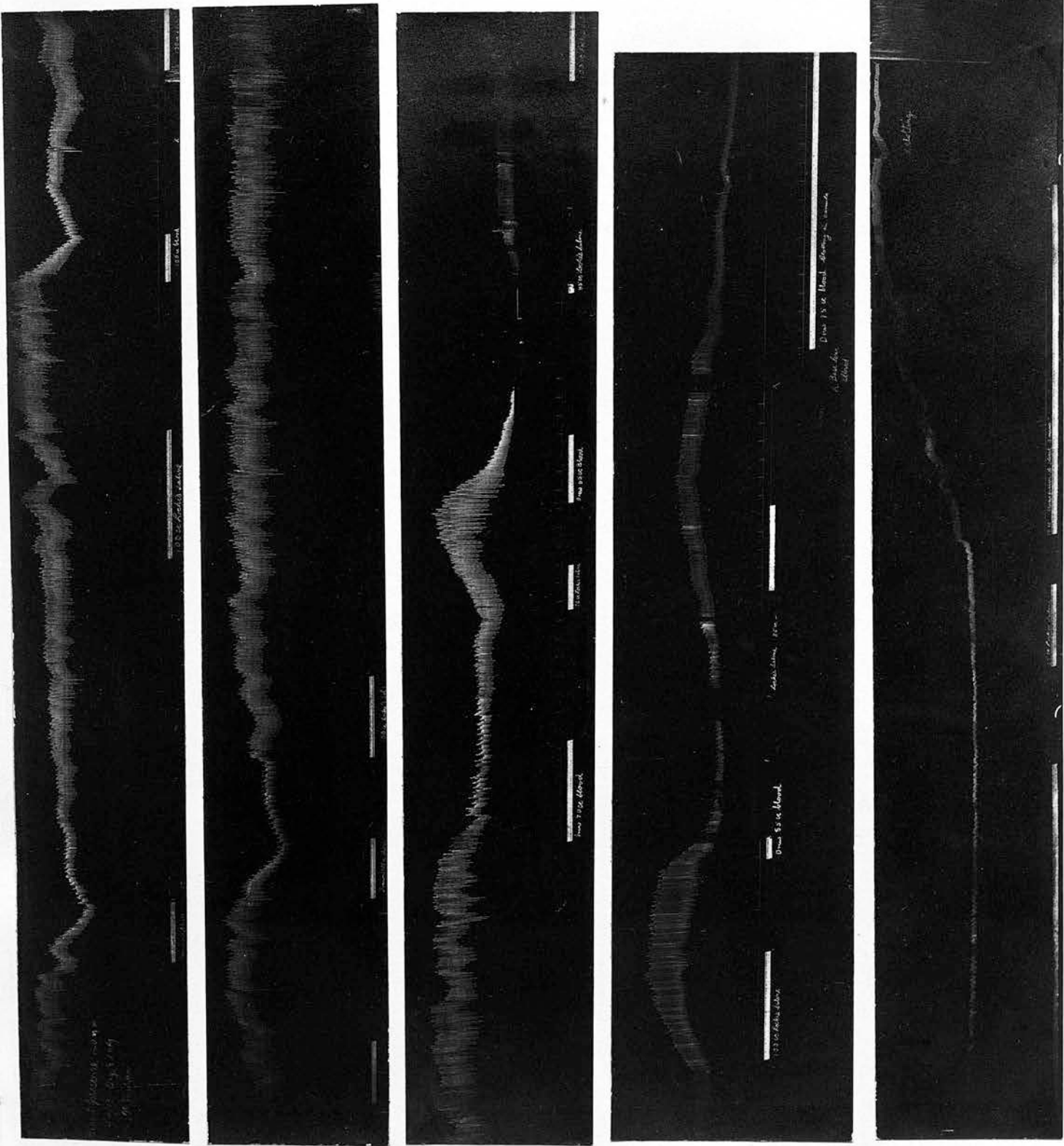


Fig. 8. Experiment V. Blood pressure tracing showing the effects of bleeding, infusion of saline & transfusion of blood.

Comments:- As in Experiment 4 it was noted that after withdrawal of a given amount of blood, the blood pressure could be restored to the normal or almost to the normal level, by infusion of the same amount of saline. The immediate fall of blood pressure which occurs after a copious bleeding from a large artery like the femoral is only temporary, as the vessels soon adapt themselves to the diminished volume of blood. Following the rapid diminution of blood pressure, there is a tendency for the pressure to rise again towards the previous level. After several bleedings, the effects of saline infusion become much less marked, and there may be practically no alteration in the blood pressure. By continuing the infusion of saline so that a greater amount is given than of blood which has been lost, the blood pressure may again be raised to a marked extent. A stage is reached, however, when it is impossible to keep the animal alive by simple infusion of saline, owing to the extreme dilution of blood, and consequent diminution of red blood corpuscles. By the method adopted of alternate bleeding and transfusion with saline, it is possible to withdraw more blood, and to reduce the animal to a greater degree of exsanguination than if the blood pressure/

pressure had not been maintained by introduction of fresh fluid into the circulation during the bleeding. The method of withdrawing blood at intervals further permitted a more gradual and more complete depletion of the animal. Before transfusion was commenced, the animal was reduced to a condition which from dilution of the blood and loss of corpuscles, was incompatible with life. The mucous membranes were pallid, and in addition to the reduction in the blood pressure, the force and volume of the pulse were extremely small, and in a given time only a relatively small amount of blood could be withdrawn by bleeding. The respirations were embarrassed by deficient oxygenation.

The main result of the repeated bleedings was to depress the activity of the vaso-motor centre through oxygen-want, and also to lower the muscular tone of the heart through the lowering of the blood pressure, and the diminished blood supply. After excessive haemorrhage, saline fails to restore the vitality of the vaso-motor centre, and also fails mechanically to maintain the blood pressure. Transfusion of blood has an immediate effect on the condition of the animal, by mechanically raising the blood pressure, and by restoring the vitality of the vaso-motor centre.

Conclusions//



Conclusions from experiments on transfusion:-

- (1) Paraffinned glass canulae can be safely and successfully used for arterio-venous transfusion in dogs.
- (2) The short duration of the transfusion in dogs, averaging from two to three minutes and the large size of the donors' arteries do not permit the conclusion that a similar canula would be successful in human cases.
- (3) When the operation is performed with aseptic precautions, the animal makes a good recovery, and in the case of dogs, the transfused blood maintains its physiological function.
- (4) When the amount of haemorrhage is moderate, infusion of normal saline, (Locke's solution), will restore the blood pressure practically to the normal level.
- (5) After repeated haemorrhages at short intervals, which have reduced the animal to a profound degree of exsanguination, infusion of saline fails to raise the blood pressure, and to resuscitate the animal.
- (6) Transfusion of blood is an ideal treatment for the constitutional symptoms of primary haemorrhage in dogs.
- (7)/

- (7) Transfusion of blood will raise the blood pressure mechanically, and will restore the activity of the vaso-motor and other vital centres, after excessive haemorrhage, when saline has failed to do so.
- (8) An animal reduced to a moribund condition by repeated haemorrhage can be immediately resuscitated by transfusion of blood.
- (9) An animal infused with saline after a moderate loss of blood makes a more gradual recovery after the operation than an animal which has been restored to its normal condition by transfusion of blood after excessive haemorrhage.

Description of methods employed by the Writer for the  
transfusion of blood in clinical cases;

The first clinical application of transfusion was made on December 12th, 1913, in a case of Pernicious Anaemia, after the necessary experience of the technique had been gained by experiments on animals. Since that date, I have had many opportunities of performing transfusion of blood for a variety of surgical and medical conditions and of trying different methods.

The/

The first method which was employed was a direct arterio-venous transfusion. The radial artery of the donor was connected to the recipient's vein by a paraffinned glass canula, similar to that first used by Brewer and Leggett<sup>23</sup> in 1909. Paraffinned glass canulae had proved quite satisfactory for experimental transfusions in dogs, and it was decided therefore to try them in the clinical cases. A short experience was sufficient to show that they were not entirely satisfactory, and in subsequent cases, when direct transfusion was required, paraffinned metal canulae were used in preference. The fact that glass canulae are transparent is no advantage as the occurrence of clotting can only be observed by the absence of pulsation in the vein beyond, or by noting that the vein is firmer on palpation. Further, in order to fix the glass canulae in the vessels, it is necessary to have a slight bulbous thickening of the tube at either end as is shown in the illustration. (Fig. 9a. )

The lumen of a glass tube is necessarily irregular unlike that of a simple metal canula, which can be grooved on the outer surface only. When using the radial artery, it is necessary to employ a canula with the largest possible lumen, and a metal canula of a given external diameter has a larger lumen than a glass canula of the same diameter. In subsequent cases/

cases of direct transfusion, metal canulae were therefore employed, and these were found quite satisfactory. In certain cases however, it was found that there was a tendency for the canulae to slip or be pulled out of one or other of the vessels. To prevent this, the canulae at first were grooved and tied in with silk, but in restless patients it was sometimes impossible to prevent a considerable strain being placed momentarily upon the junction. It was impossible to thicken the wall of the canula sufficiently to provide deep grooves, owing to the small size of some patients' radial arteries, so that till the method of fixing the canula in the vessels was modified, there was always some anxiety lest it should be pulled out of the artery or vein.

In order to secure the canula firmly, in the recipient's and donor's vessels, so that no strain could dislodge it, I introduced special forceps; (Fig. 10c.) for clamping either end of the canula where it was included in a vessel. The method of using this forceps is shown in the illustration (Figs 12 & 13) The blades of the forceps were doubly grooved near the tip, so as to include when clamped the whole of the end of the canula within the vessel. The forceps also provided a useful means of steadying the canula, and preventing kinking of the vessels during transfusion; and they also did away with the necessity/



necessity for grooves or ridges upon the ends of the canulae. It was therefore possible to use metal tubes with the thinnest possible wall, and the largest internal diameter. A pair of Kocher's forceps will fix the canula in the vessels if the special forceps are not available.

Although paraffinned metal canulae proved adequate for joining the vessels of the donor and recipient together, considerable difficulty and delay was sometimes experienced in tying the end of the canula into the recipient's vein, after it had already been fixed in the donor's radial artery. This difficulty depended on the general condition of the patient, and the size of the vein. In cases of pernicious anaemia, the superficial veins are much smaller than in cases of primary haemorrhage or secondary anaemia, and the vein may have to be stretched before the canula can be admitted. The small size of the vein, however, does not offer such an obstacle as does restlessness on the part of the patient. Some of the cases of pernicious anaemia which I transfused by the direct method were semiconscious at the time, and as they were often unable to appreciate what was being done, were apt to resist or to move the arm before the junction could be completed. I decided therefore to try a double canula in order to simplify the/

the operation, and found that the double canula worked well in practice.

The two halves of the double canula (Fig. 9. ) were introduced separately into the donor's artery and the patient's vein respectively, and were firmly clamped by the special forceps. When this step of the operation had been completed, the patients' arms were approximated, and the separate halves of the canula were joined. No special lock was found necessary to maintain the junction, as the fixation forceps were applied at the same angle, and proved a convenient means for keeping the two halves of the canula together.

With the double canula, considerable time can be saved, as the operator and his assistant can each expose a vessel, and insert the separate halves of the canula. The position of the patients' arms can be finally arranged after the preliminary steps of the operation have been completed.

Although with the double canula direct transfusion could be performed with little difficulty, and with practical certainty of success, the operation entailed considerable inconvenience on the part of the donor. This objection is more valid than the fact that the amount of blood cannot be measured, and it seemed a sufficient reason to try the methods of indirect transfusion from vein to vein, revived by/

by Lindemann, Unger and others. It is always easier to expose a superficial vein on the donor's arm than the radial artery. A small incision is quite sufficient, and in some cases it is possible to withdraw the blood by means of a suitable needle without incision. The instruments used for vein to vein transfusion were designed for use both with the simple syringe method, and for the employment of a syringe connected to the canulae by a two-way stop-cock.

When the simple syringe method is used, separate canulae are inserted into the donor's and recipient's veins, and a series of syringes is used as a means of rapid transfer from one to the other. In the case of the donor, it is as a rule unnecessary to make an incision, unless the vein is small or inconspicuous, or unless a large amount of blood is required; in which case it is safer to expose the vein and tie in the canula. It is advisable to expose the recipient's vein by incision, and to tie the canula in place. In most cases of anaemia, such as are likely to require transfusion, the patients' veins are either small or are collapsed, and it is frequently impossible to demonstrate them. Further, there is always the risk of the sharp point of the needle altering its position during the time necessary for transfusion, and if the wall of the vein be punctured, or if/

if clotting should occur in the needle, the latter will have to be withdrawn, and in all probability there will be clotting in the donor's canula before a fresh needle can be inserted into a vein of the recipient. I therefore used special needle canulae which could be directly inserted into the donor's vein, provided with a short rubber connection to fit the syringes. Simple metal canulae were used for the recipient's vein, or for the donor's vein, in cases where it was thought advisable to expose the vein by incision.

In using the simple syringe method, little time can be lost if the risk of clotting is to be prevented, and therefore a number of syringes must be passed in rotation from the donor to the recipient; this requires several assistants. The following experiment upon a dog shows the necessity of frequently changing the syringe.-

Object:- To find how long a syringe can be used to withdraw and reinject blood without clotting.

Method:- A 10 cc. Record syringe was prepared by first coating it inside with vaseline, and then running it through <sup>with</sup> liquid paraffin.

The right external jugular vein was exposed, and clamped in two places. It was then opened between the clamps, and washed out with saline and liquid paraffin.



A canula connected to a short length of rubber tube was then tied in, and secured with a pair of Kocher's forceps. A fitting for the nose of the syringe was attached to the other end of the tube. The left external jugular vein was now exposed, and clamped to increase the pressure in the right. The syringe was now connected to the fitting, and the peripheral clamp on the external jugular removed.

Result:- From 11.12 a.m. to 11.16 a.m., 270 cc. of blood were withdrawn and reinjected before signs of clotting occurred. A small clot was afterwards found in the syringe.

Conclusion:- In clinical practice, the syringe should be frequently changed to prevent any risk of clotting or of incipient clotting.

Addendum:- It was found that the coagulation time of 5 cc. of blood from the last syringe-ful was 50 seconds. Fresh blood clotted in 5 minutes 20 seconds.

The syringe method is a practicable and reliable one, but it can be still further simplified, by employing a single canula or tube between the veins, with an intermediate two-way stop-cock, to which the syringe is attached. The first instrument of the/

the latter type which I used was a U-shaped metal tube one end of which was tied into the recipient's vein, while the other end was either tied into the donor's vein, or else joined to the needle canula, the end of which it was made to fit. In this instrument the syringe was connected to the stop-cock at right angles. By turning the tap through half a circle, the syringe could be alternately connected through the canula with either the donor's or recipient's vein. Although this arrangement facilitated the rapid withdrawal and reinjection of blood, there is bound to be more risk of clotting from the greater length of tubing through which the blood has to flow, and from the presence of the stop-cock, than in the simple syringe method. To provide for this risk, a connection was added through which saline could be injected at intervals if found necessary. The syringe canula method with two-way stop-cock proved satisfactory for transfusions of moderate amounts of blood. Several modifications of the original instrument were made and employed, and these will be described later.

Whatever the relative merits of arterio-venous and vein to vein methods of transfusion, there is no doubt that in infants the latter is the method of choice. Only a small amount of blood is needed, and the simplest method of all is to use a syringe for/

for the purpose. If the anterior fontanelle is still open it is usually easy to insert the needle directly through the skin into the longitudinal sinus. In older children, or if it is thought undesirable to puncture the fontanelle, it is necessary to tie the canula into the external jugular or other superficial vein. In any case, the blood can be readily injected by means of a syringe. Citrated blood could also be used for this purpose, but there is no obvious reason why it should be preferred to whole blood, as the small amount necessary makes the syringe method both simple and safe. With a suitable needle there is as a rule no difficulty in injecting fluids into the longitudinal sinus, as it is usually easy to feel when the point of the needle has entered the sinus, and venous blood begins to drop from the needle.

Although the syringe canula method has proved in my experience to be the most rapid method of performing transfusion of blood, it entails immediate contact between the donor and recipient which, although rarely upsetting either party, is not always convenient. In certain cases it may be necessary to transfuse blood during an operation, and neither direct arterio-venous transfusion nor vein to vein transfusion with canulae as described above are so suitable as methods which permit the blood to be collected in another room. For this purpose citrated/

citrated blood is well adapted, as well as for the routine transfusion of ordinary cases. The fact that citrated blood can be kept for some time without risk of clotting makes it more valuable than any other method in certain cases. In cases of shock and haemorrhage which require operation, where it is considered that transfusion may be necessary, citrated blood makes it possible to transfuse at the psychological moment. It is also possible to transport citrated blood for some distance. These advantages of the method are confirmed by my own experience. Transfusion with citrated blood proved particularly valuable in a case of severe secondary haemorrhage from the axilla following a gunshot wound. The haemorrhage was excessive, and the patient was reduced to a profound condition of collapse, both by the immediate haemorrhage and by his general condition. He had already been much reduced by septic absorption and by repeated haemorrhages from the brachial artery. The haemorrhage had recurred, in spite of ligation of the third part of the subclavian artery as well as of the original wound in the brachial. Several of the fingers were gangrenous and the arm was paralysed. There were several large discharging wounds in the shoulder region. As the bleeding could not be controlled, except by digital pressure through a granulating/



granulating wound in the axilla, it was obvious that the haemorrhage could only be arrested satisfactorily by disarticulation of the shoulder. As his prospects of recovery from such an operation seemed extremely remote, a suitable donor was selected after examining the blood of several of his fellow patients by agglutination tests, and 700 cc. of blood were prepared by the citrate method. It was decided to reserve the transfusion for the period of the operation, or to inject the blood later as indicated at the time. Intravenous and subcutaneous salines were given at once, and the transfusion was commenced early in the operation, as otherwise it seemed doubtful whether the patient would survive its completion. The transfusion was finished at the same time as the operation, which did not take long, and the immediate effect was an improvement both in the blood pressure and in the patient's colour. His condition on returning to bed was undoubtedly better than before the operation, and he continued to improve steadily, till a fortnight later, when a fresh profuse haemorrhage occurred, which was controlled by ligature. On this occasion the patient was again transfused, and made an uninterrupted recovery. There is no doubt in this case that the readiness with which the citrated blood could be administered at the right moment/

moment was the most important factor in the choice of method. In other two cases it was possible to transfuse a private patient in his own home with citrated blood collected from a donor in hospital. Although the donor might have been taken to the patient's bedside, as the case was urgent, it was thought that time could be saved by collecting the blood in hospital, where the necessary instruments and solutions were ready sterilised. The flask containing the blood was surrounded with cotton wool, and transported by motor car; the transfusion was completed with the minimum of delay and with a successful result.

Having briefly mentioned the different methods which I have used for transfusion, I will now describe the details of the instruments, and the technique adopted in operating with the various methods.

#### A. Direct arterio-venous transfusion.

This operation was performed on twenty-one occasions. The radial artery was connected to the recipient's vein by a short canula.

Description of canulae.

I. Glass canulae. These were used in two cases.

The canulae were similar to the tubes used in the experiments on dogs, and are shown in Fig. 9. They were prepared by a glass blower, the walls being as thin as/

as was consistent with strength. Several canulae of different lengths were prepared before the operations. The length of the canulae varied from 40 mm. to 70 mm., and their ends were bevelled, so that they could be easily introduced. The external diameter of the canulae varied from 2 mm. to 3 mm. The following preparation of paraffin was used for coating the tubes:-

Hard paraffin	2 parts.
Soft paraffin	2 parts.
Stearin	1 part.

The paraffin mixture was melted and sterilised in a porcelain dish over a Bunsen flame, and the glass tubes were left in this mixture at a temperature of  $100^{\circ}$  C. for a few minutes. The canula was then picked out with a pair of forceps, and the melted paraffin allowed to run off. As the tube cooled, a thin coating of paraffin was left on the inner surface. There is a tendency for the last drop of the paraffin to close the end of the tube, but this was easily prevented by wiping the ends of the canula on a piece of sterile wool. The coating of paraffin did not appreciably diminish the lumen of the canula. After the canula had been coated, they were immediately placed in sterile stoppered test-tubes, and were then ready for use at any time.

II. Metal canulae. These were used in five cases. They varied in length from 40 mm. to 55 mm. and were made of German silver. Their internal diameter varied from slightly under 2 mm. to slightly over 3 mm. Several different forms of canula were tried, and the first of these was kindly supplied to me by Mr Cathcart. In some, the ends of the tube were bevelled, in others plain; and all were lightly grooved in order to make the ligation more secure. The metal canula which I finally found most useful, in conjunction with the special forceps for fixing it in the vessels, is shown in Fig. (Fig. 9), and was 55 mm. in length, with both ends bevelled, and ungrooved. It was generally sufficient to have two canulae of this type prepared for an operation, with an external diameter of 2 mm. and 3 mm. respectively. The larger canula was used if the radial artery was sufficiently large to admit it.

The metal canulae were coated with paraffin, and stored ready for use in the same way as has been described for the glass canulae.

III. Double metal canulae. These were used in fourteen cases. The advantage of having a canula in two pieces has already been explained. Each half of the canula could be separately tied into its proper vessel, //



vessel, and the junction of the two halves provided a simple method of completing the anastomosis. The total length of the canula was 55 mm. and two sizes of 2 mm. and 3 mm., external diameter respectively, were found sufficient to fit any radial artery. The two halves of the canula were prepared from a single tube of uniform diameter, and consisted of a male and a female portion, turned to fit one another exactly, so that the lumen had a continuous smooth surface. The double metal canulae were prepared at first with a paraffin coating in the same way as described above, but this did not prove entirely satisfactory. In spite of the greatest care there was apt to be slight irregularity in the paraffin coat at the line where the two halves joined. Preliminary lubrication of the canula with vaseline and liquid paraffin was found more satisfactory.

The following description of direct transfusion refers to the technique employed when the double metal canula is used. From my experience I believe that this is the simplest and most efficient method of performing direct transfusion.

Direct/

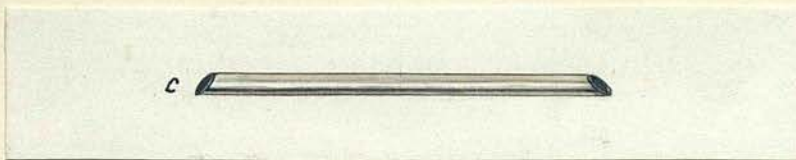
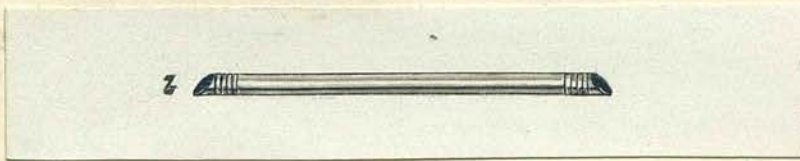
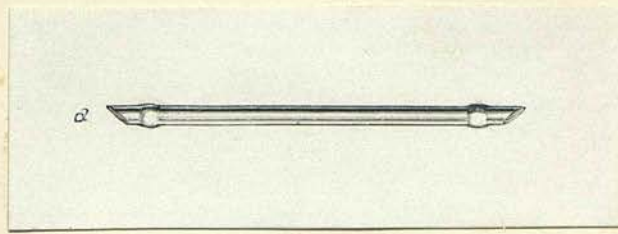


Fig. 9. Canulae used for direct transfusion.-  
 (a) Glass canula.  
 (b) Metal canula with grooved ends.  
 (c) Metal canula - not grooved.  
 (d) Double metal canula.

Direct arterio-venous transfusion : Technique  
of operation.

I. Instruments used.

The only special instruments needed, in addition to the canula, were:-

Three or four pairs of fine pointed artery forceps.

Two pairs of fine pointed dissecting forceps.

Two light clamps for temporarily controlling the vessels. Fig. 10.

A pair of fine pointed scissors, with narrow blades.

Two glass pipettes with rubber teats, for washing out the vessels with saline and liquid paraffin.

Two special forceps for fixing the ends of the canula within the vessel. Fig. 10.

II. Selection of donor's and recipient's vessels.

The donor's left radial artery was usually selected. The selection of the vein in the recipient depended upon several factors.

Other things being equal, a superficial vein in front of the left elbow was chosen. The median cephalic is perhaps the most suitable, as it permits easy adaptation of the arms, but if the median basilic appeared to be larger, it was preferred. In cases of/



of primary haemorrhage it is always easy to find a suitable vein in front of the elbow, but in cases of chronic anaemia, and particularly in cases of pernicious anaemia, the superficial veins of the arm may be extremely small and thin, and I have found it necessary to expose the basilic vein. In cases however where the superficial veins in the front of the arm cannot be demonstrated, the external jugular vein is easily found, and is usually of ample diameter to admit the transfusion canula; In cases where the transfusion was made into the external jugular vein, it was noted that the patient reacted more quickly than when a peripheral vein was used. The external jugular vein is easier to find than the internal saphenous, and in chronic cases of anaemia the latter vein was never employed.

III. Position of patients. In a typical case, when the transfusion was done from the left radial to the left median basilic or cephalic vein, the donor and recipient were placed on parallel tables, lying in opposite directions with the left arms abducted to a right angle, and sufficiently apart to bring the donor's wrist opposite the antecubital region.

For transfusion into the external jugular vein, the donor's table was placed at right angles to the head/



head of the recipient's table, and the arm of the donor was brought into position by abducting it to a right angle.

When the vein in the right arm or the right side of the neck has to be selected, the relative positions of the donor and recipient can be altered accordingly.

There is no doubt that the maintenance of asepsis requires special care during the operation, as there is considerable scope for errors in technique through derangement of towels, in the somewhat awkward and cramped position of the patients.

IV. Anaesthetic. 1% novocain was used in all the cases for infiltrating the tissues.

In one or two of the early cases where adrenalin was used, it was found that the flow of blood from the radial artery was much diminished by spasm. It is therefore inadvisable to use any vaso-constrictor with the local anaesthetic.

V. Exposure of vessels. It is preferable for the operator and his assistant to expose and prepare the radial artery and the recipient's vein simultaneously; but if this is not possible the recipient's vein should be exposed first.

An incision of  $1\frac{1}{2}$  to 2 inches is ample for exposure/

exposure of the radial artery, immediately above the wrist, and no difficulty is met with in doing this. Generally two or three minute branches have to be caught and ligated or twisted, and the accompanying veins may need to be separated..

VI. Preparation of vessels for canulae. Both vessels should be exposed before either is opened, and the recipient's vein should be prepared first. Only  $\frac{1}{2}$  to  $\frac{3}{4}$  inches of the vein needs to be exposed. The vein is ligated distally, clamped proximally, opened with a V-shaped snip by scissors, washed out with saline and liquid paraffin, and is then ready for the introduction of the canula. Occasionally it is necessary to divide the vein, but as a rule it is better not to interrupt its continuity. As much of the radial artery should be exposed as the length of the incision will permit. After ligating the artery distally, it should be lightly clamped as close to the proximal end of the wound as possible. The artery may either be divided immediately above the ligature, or opened obliquely with scissors at the same point. I have tried both methods, and believe that it is better not to cut the artery completely across. All trace of blood is then washed out with saline and paraffin.

As the size of the radial artery varies within considerable/

considerable limits, it is often necessary to stretch the lumen gently with a pair of fine mosquito forceps before the canula can be slipped into place. The end of the canula is then fixed in position by a ligature, and finally secured by applying the special clamp forceps which I introduced for this purpose. The second half of the canula is introduced proximally within the vein, and secured in the same fashion. Having completed these preliminaries, the position of the patients' arms is adjusted. Before joining the canula, it is advisable to fill the lumen of the tubes and of the vessels with normal saline, although there is no reason to expect that any symptoms would result from the slight amount of air which might enter the recipient's vein if this were not done. The two parts of the canula should be kept from separating by holding together the fixation forceps, which, if they are suitably applied, form convenient handles. Both at the commencement, and during the transfusion, the patients' arms must be held firmly together, because even slight traction may narrow the radial artery, and diminish the flow of blood. Movements are apt also to cause kinking, and interference with the flow.

The clamp controlling the recipient's vein is removed first. When the flow starts, the recipient's vein becomes moderately distended, and if inspected closely/

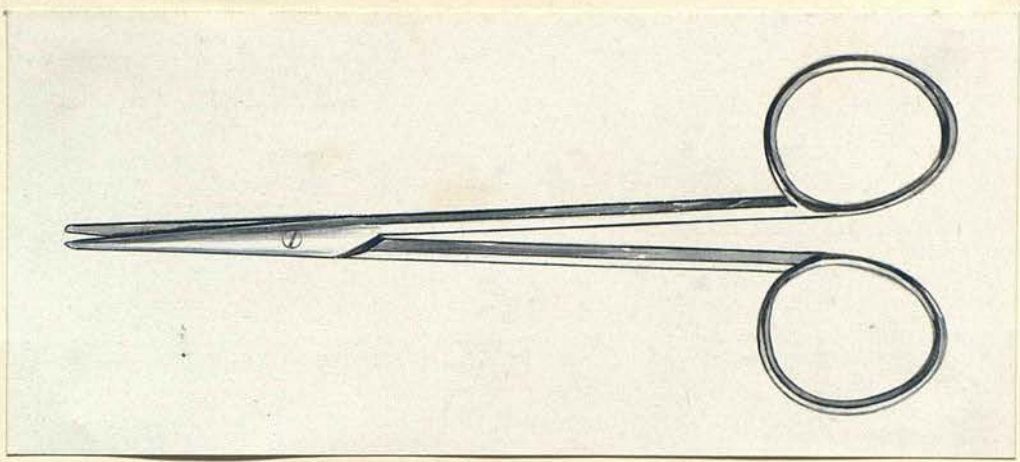
closely the vein can be seen to pulsate. By gently palpating the vein, the pulsation, which is transmitted from the artery, can be felt, and the amount of blood which is passing can be roughly estimated by noting the strength of the pulsation of the vein.

The duration of the transfusion will depend mainly upon the size of the radial artery. Within a few minutes, the patient's colour may be markedly improved and within a quarter of an hour the donor may already show signs of loss of blood. In other cases, when the artery is small, and the smaller size of canula is used, the transfusion may be continued for half an hour or more without causing symptoms in the donor. As a rule, however, after half an hour there is a tendency to clotting in the canula, generally in the donor's end. If it is thought necessary to continue the transfusion after the occurrence of clotting, the vessels should be clamped and washed out with saline and liquid paraffin after removal of the canula. A fresh canula can then be employed. As a rule it is not possible to transfuse much longer after clotting has occurred. In most of my cases of direct transfusion, blood was still flowing when the operation was concluded, and the transfusion was generally stopped either because the recipient was sufficiently improved, or because the donor had lost/

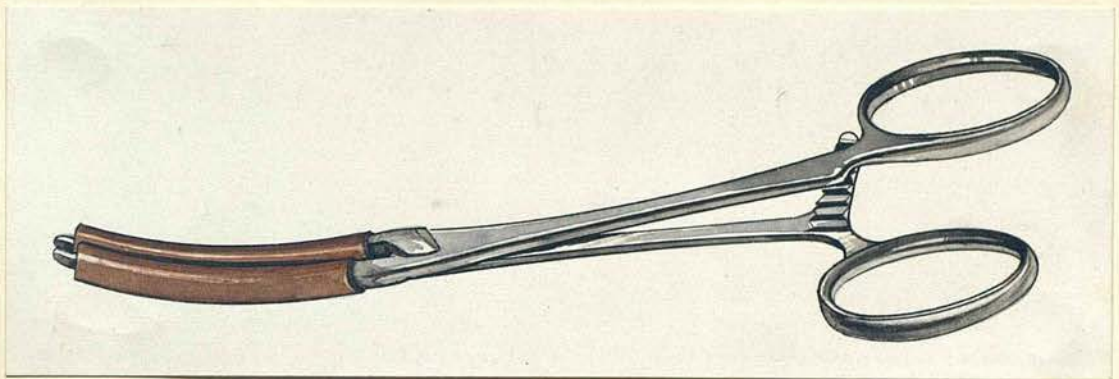


lost as much blood as he could safely afford. At the conclusion of the operation, the vessels were ligatured, and the wounds closed in the usual manner.

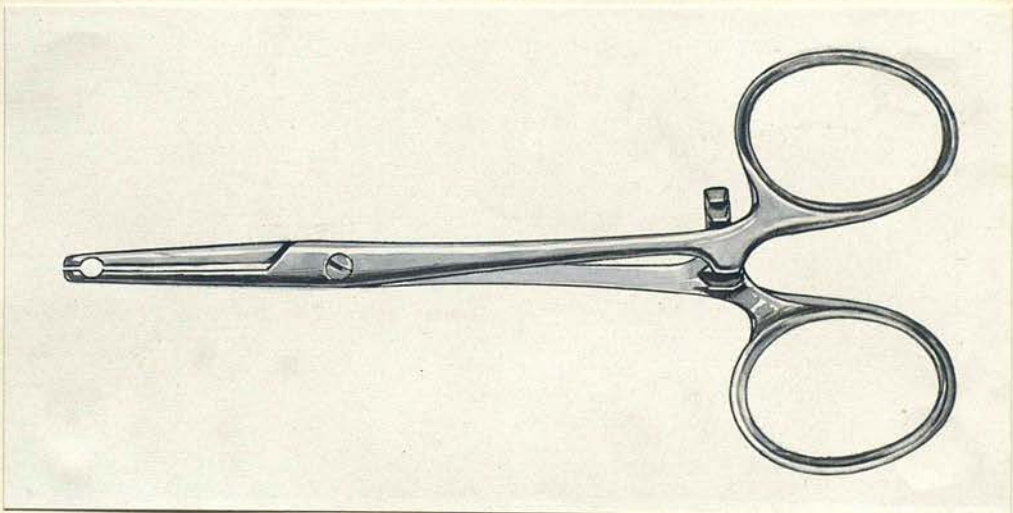
VII. Comments. The impression obtained from the twenty-one cases of direct transfusion performed with the canulae and instruments described above was favourable, and I think it can be claimed that direct transfusion with the double canula is both reliable and effective. There is no doubt that the metal are better than glass canulae, and that the double canula simplifies the operation. No case of sepsis occurred in the series of cases, and the risk of air embolism is excluded. The occurrence of clotting towards the conclusion of the operation was almost entirely limited to the instrument; any clot which formed was firmly attached, and none of the cases presented symptoms suggestive of intravenous thrombosis or embolism. With the exception of Crile's method of exact apposition of the intima of the vessels, the double canula affords a means of transfusion of whole blood with a minimum risk of complications. As compared with my subsequent cases of transfusion with venous blood, I formed the impression that immediate improvement was more marked when arterial blood\* was used, but that there was no obvious difference between the two methods in the/



a



b



c

Fig. 10. Instruments used for direct transfusion with metal canulae.  
 (a) Scissors.  
 (b) Clamp.  
 (c) Fixation Forceps.



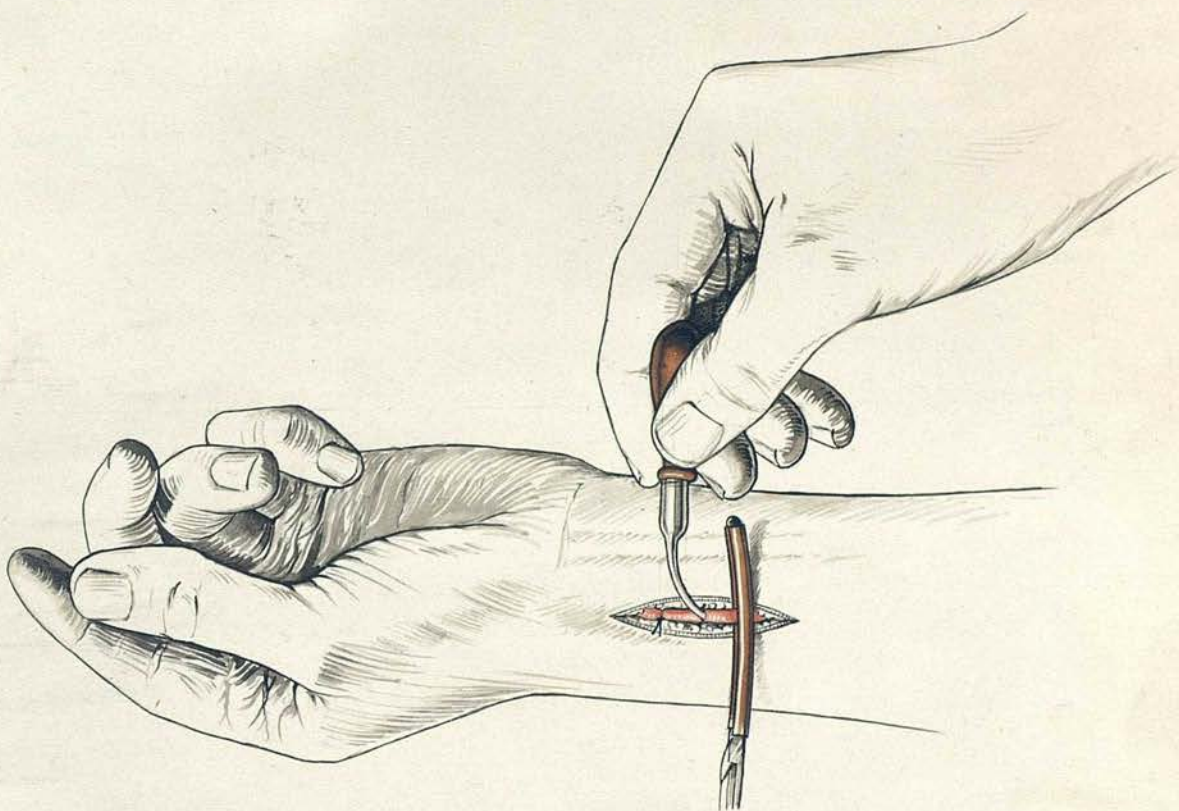
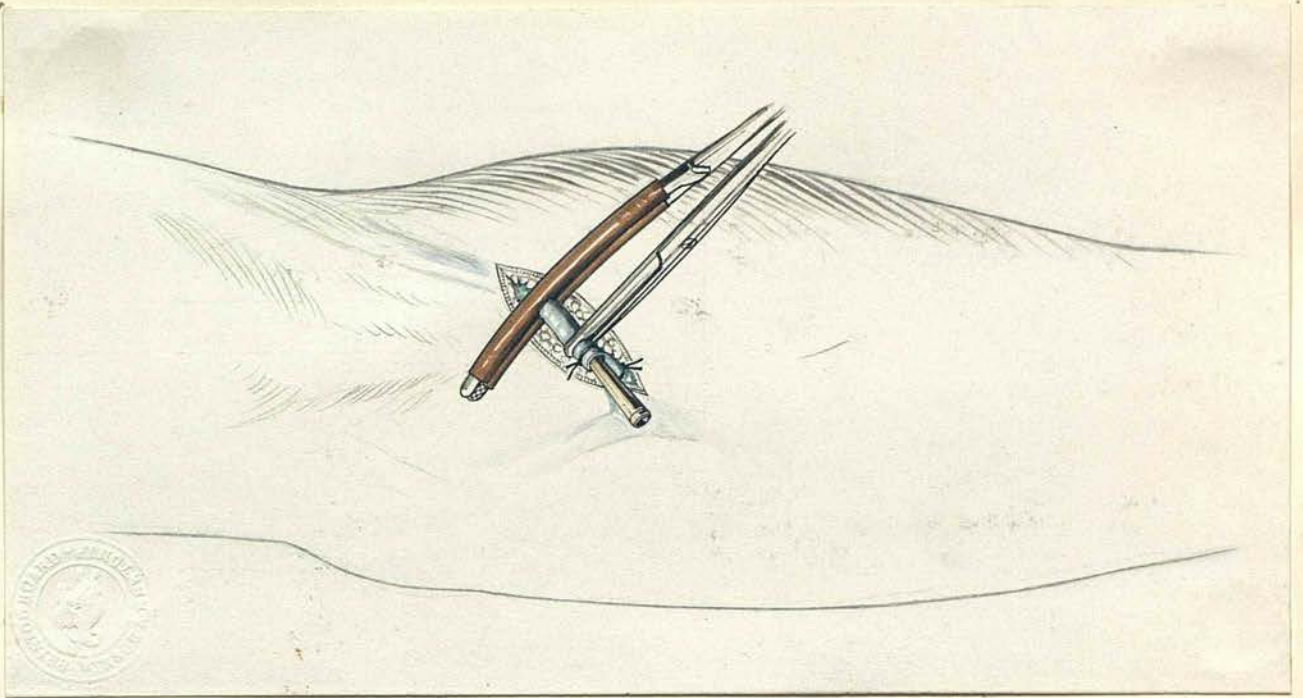
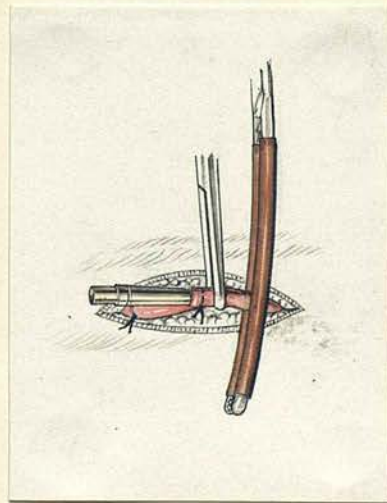


Fig. 11. Direct Transfusion. Lubrication of radial artery.



a



b

Fig. 12. Direct Transfusion with double canula showing.-  
 (a) One half of canula fixed in recipient's vein.  
 (b) Remaining half fixed in radial artery.



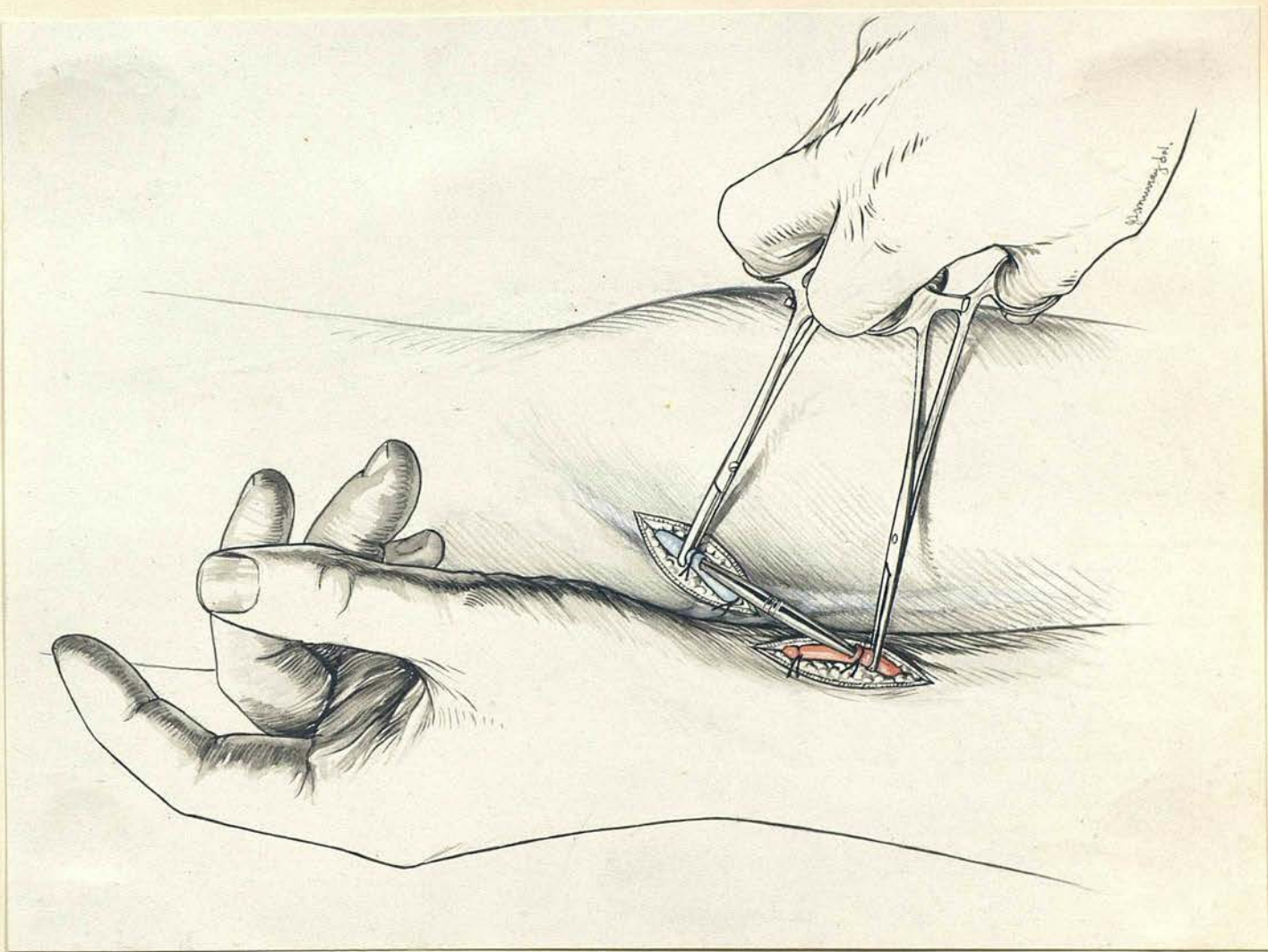


Fig. 13. Direct transfusion with double canula showing operation completed.

the final results. Three possible disadvantages are mentioned which are not necessarily present with other methods. The choice of the radial artery incapacitates the donor longer from work than if he is bled from a superficial vein. The method necessarily requires close contact between the patient and donor, and in emotional circumstances this may be a disadvantage. More stress has been laid by some observers on the fact that by this method it is impossible to measure the blood transfused. While in some respects this objection to the method is valid, I do not consider that it is as important as the objection to the use of the radial artery. It is apt to be forgotten that in injecting a known amount of blood the volume of the recipient's blood with which it is to be mixed remains unknown. After all, the amount required can only be estimated by judging the effects of the transfusion upon the patient, and this may be done by noting the change in the patient's appearance, and by estimating the haemoglobin.

#### B. Indirect transfusion from vein to vein.

Although direct transfusion from vein to vein by apposition of the intima of the two vessels can be carried out by an instrument such as that employed by Sorresi, the absence of pulsation in the donor's vein/

vein must render it difficult sometimes to be certain that the flow of blood continues; I have therefore not made use of this method for transfusion, preferring the use of a syringe and canulae either with or without a two-way stop-cock. Since 1916 I have used one or other of the various methods of vein to vein transfusion, partly because of the simplicity of the operation, and partly because of the slight inconvenience which it causes the donor.

Indirect transfusion with syringes and simple canulae.

This has been used in seven cases.

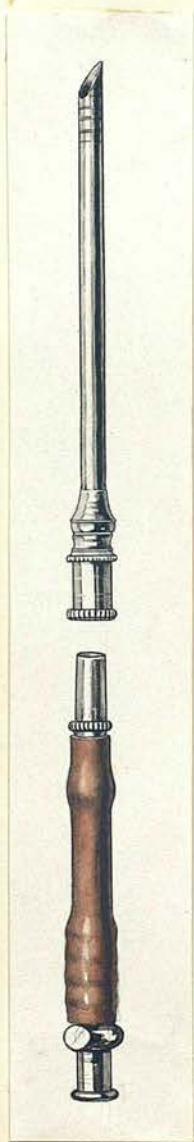
At least four 20 cc. Record syringes should be used, and

I have found this number ample.

Needles and canulae:- As previously mentioned, it is advisable generally to tie a canula into the recipient's vein, and it may be necessary to do so also in the case of the donor; but when the donor's vein is large, needle-canulae can be used perfectly well without incision.

The canula which I have used for tying into the vein in these cases is a short tube of German silver 30 mm. in length. (Fig. 14c.) The outside diameter of the tube is 4 mm. A short piece of rubber tubing, two or three inches in length, is attached to the canula/





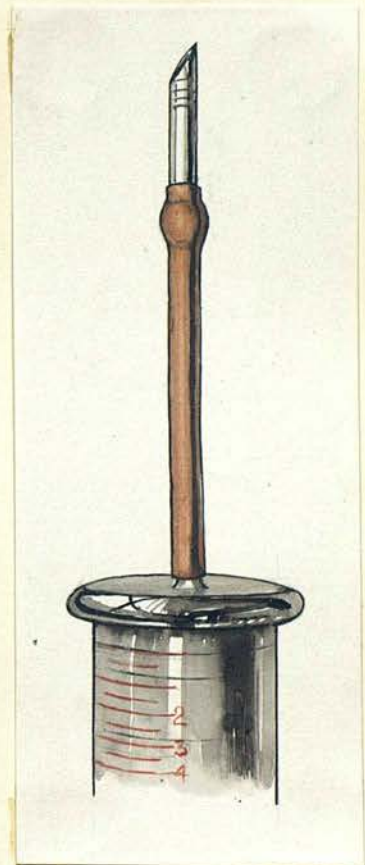
A



B



C

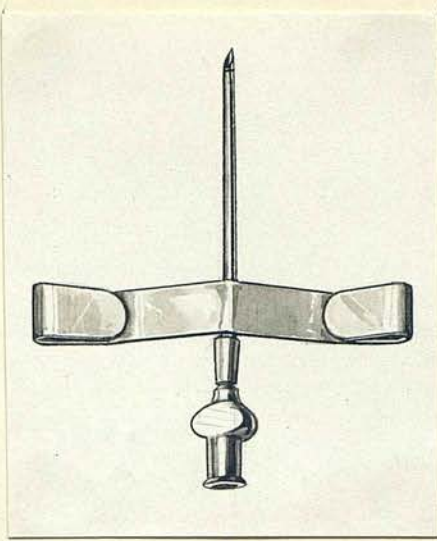


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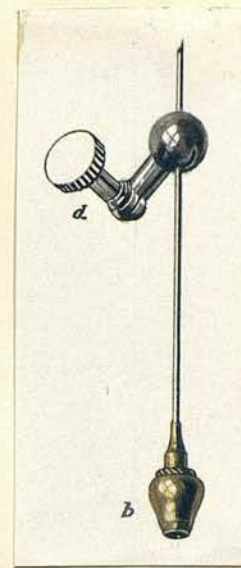
Fig. 14. Indirect Transfusion. Syringe method.  
 A. and B. illustrate the first form of canula used by the Writer for this method.  
 C. and D. show the form finally adopted and described in the text.



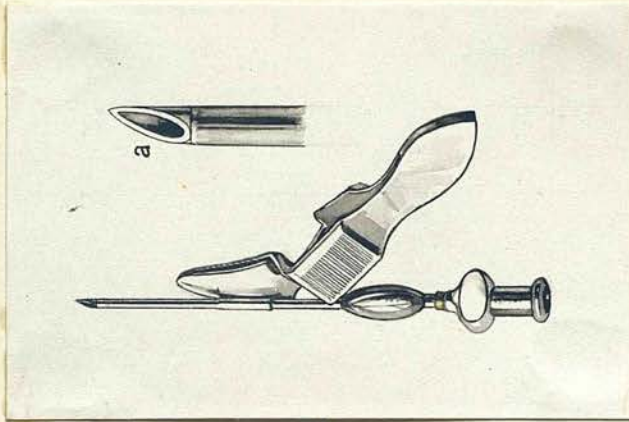
canula for connection with the syringe. When the needle canula is used, care must be taken to prevent the canula shifting its position once it has been introduced. The constant handling necessary in removing and attaching the syringe is liable to dislodge the needle, and I have used several devices for preventing this. As the sharp point of the needle would be liable to wound the wall of the vein, the needle canulae have always consisted of two tubes, one within the other. The outermost tube is in the form of a canula, the end of which is blunt, while the point of the inner tube is sharp, and projects slightly beyond the end of the canula. The sharp point of the needle is bevelled at  $35^{\circ}$ . After the vein is successfully entered, the combined needle canula is pushed on sufficiently far to ensure that the end of the canula is in the vein; the sharp inner needle is then withdrawn, while the canula is left in place, and if necessary pushed a little further in. A short piece of rubber tubing serves to connect the canula to the syringe. The form of needle-canula which I found most effective is shown in Fig. (15b.). The canula is attached to a bull-dog forceps, which can be clipped on to the skin without pain. By fixing the canula in this way there is no risk of its becoming dislodged.



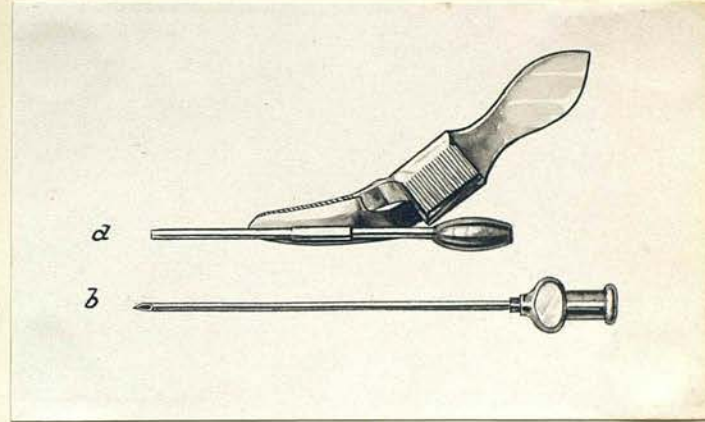
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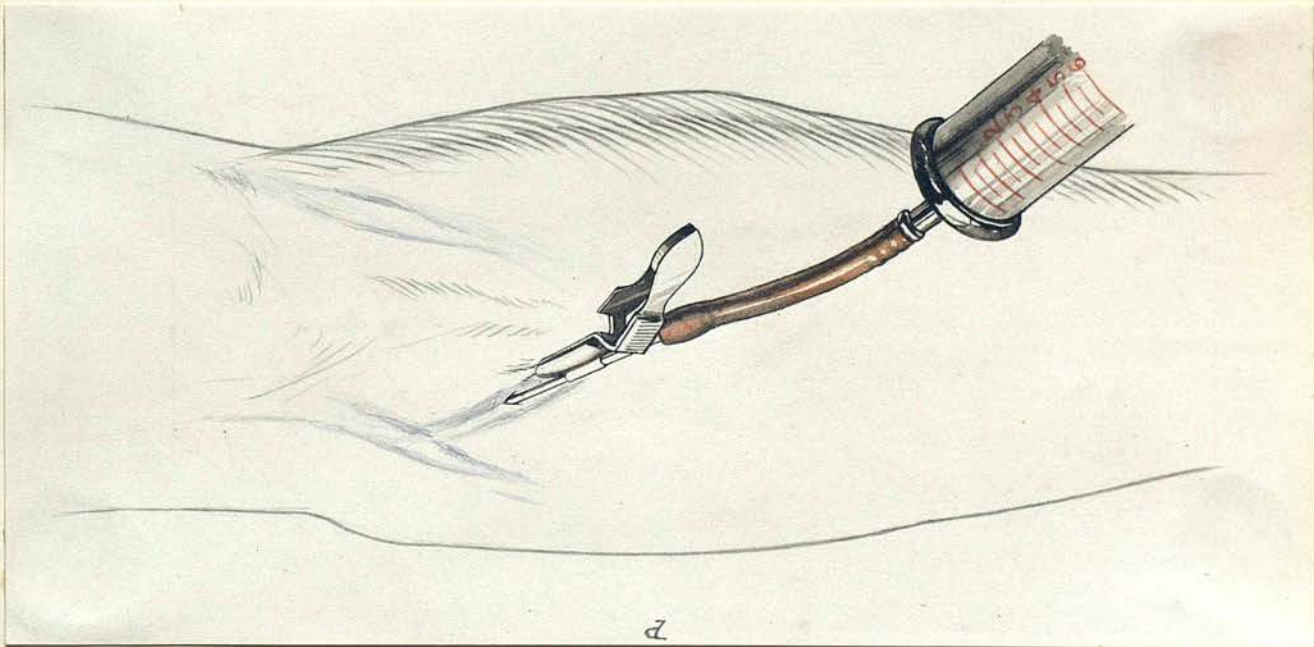
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d

Fig. 15. Needle-Canulae for indirect transfusion.  
 A. shows the first form used.  
 B. and C. illustrate the form finally adopted.  
 D. shows the needle-canula in use.  
 E. Needle for longitudinal sinus.  
 a. Sliding sleeve.

II. Technique of operation. The donor's arm is congested by a tourniquet, applied sufficiently firmly to distend the veins without affecting the pulse; and the most prominent superficial vein in the front of the arm is selected. Before puncturing the donor's vein, the recipient's vein should be exposed by a short incision under local anaesthesia. After ligating the recipient's vein distally, it is opened and the canula inserted attached to a syringe filled with saline; the saline should be slowly injected while the needle or canula is being inserted into the donor's vein.

When the donor's vein has been exposed by incision, it should be ligated proximally, and the canula inserted in a peripheral direction; but when the needle canula is used, it is usually more convenient to insert it in a proximal direction.

Both the canulae and the syringes should be lubricated with vaseline before being used. The operator requires an assistant to attend to the injection of the blood, while the former should devote himself to the withdrawal of the blood from the donor. The rubber tubes can be nipped with the fingers to prevent loss of blood, or entrance of air, when the syringes are detached or attached. By co-ordinating/



co-ordinating the rate of withdrawal of blood with the rate of its injection, no time is lost in transference. As the absence of clotting depends upon the rapidity with which the syringes are filled and emptied, a series of syringes should be used in strict rotation, and all trace of blood must be washed out with saline before the syringes are used again. One or two additional assistants are necessary for this method.

With the syringe method, I have injected varying amounts of blood, up to a total of 600 cc., and have found the results to be as satisfactory as with any other method of transfusion.

Comments:- While the measurement of the blood is not necessary for a successful transfusion, it is certainly an advantage that with the syringe method the amount is known exactly. The measurement of the amount of blood is particularly important in infants and young children. Only a small amount of blood is needed for transfusion in infants, and 50 cc. to 100 cc. are usually sufficient. Therefore a knowledge of the amount to be injected will prevent the risks of overtransfusion. I believe that the syringe method is the method of choice for infants. With larger amounts of blood, the question may arise whether clotting may not occur, and it has been suggested that the early stages of coagulation/



coagulation might be initiated by the contact of the blood with the walls of the syringe and canulae. So far, however, in the cases in which this method has been used, clotting has not occurred during the transfusion, and none of the cases have shown any signs that the blood has been altered in any way.

The simplicity of the method is one of its chief advantages, and as no special apparatus is necessary, the means for carrying it out are generally available, or they can be improvised should occasion for transfusion suddenly arise. Instead of the special needles and canulae described, short pieces of glass tubing could be used equally well, provided they were tied into the vessel.

The only essentials necessary for the syringe method are several syringes and plenty of assistance, and in this respect the operation is perhaps not as simply arranged for as some of the other methods.

Transfusion of blood in infants.

Although there are not many indications for the transfusion of blood in infants, it appears to be the method of choice for cases of haemorrhagic disease of the new-born, and its employment should also be considered in atrophic infants suffering from anaemia.

As already indicated, the simple syringe method is well suited for the purpose.

Transfusion/

Transfusion into the longitudinal sinus.

I. Instrument used. Since 1898 Marfan of Paris has used the longitudinal sinus for the intravenous injection of saline. It is also convenient for injection of other solutions such as glucose, sodium bicarbonate, and eusol, when it is desired to give these intravenously. Helmholtz<sup>29</sup>, in 1915, recommended transfusion into the longitudinal sinus in cases of haemorrhagic disease of infants.

The writer has employed this method on five occasions. Apart from the longitudinal sinus, none of the superficial veins in children can be readily penetrated with a needle without a preliminary incision. The advantage of using the sinus are its fixed position, and the fact that the walls are kept apart by the dura mater. As the sinus only lies from 2 mm. to 5 mm. below the surface of the scalp, and as the lumen varies from 4 mm. to 7 mm. in width, penetration with a needle is a simple matter. With a suitable needle one can generally recognize when the lumen of the sinus has been entered.

The needle (Fig. 15e.) which I have used for the superior longitudinal sinus of an infant is 60 mm. in length, and 1.25 mm. in diameter. The point/

point of the needle is bevelled at  $45^{\circ}$  and is 1.25 mm. long. It is mounted with an adjustable sliding sleeve, so that the needle, after introduction, may be firmly held against the scalp, and prevented from penetrating too deeply. The needle is connected to a 20 cc. Record syringe by a thick walled rubber tube about 20 cm. in length, and the whole apparatus is lubricated with vaseline oil before use.

II. Technique of operation. The child is wrapped in a shawl, and the head is firmly held with the sagittal suture vertical. In the case of infants, the mother should be chosen as donor, as, according to Sydenstricker,<sup>30</sup> for at least two years the infant's and the mother's blood belong to the same group.

A suitable vein in the donor's arm is selected, and a tourniquet is applied. The scalp is disinfected with spirit and biniodide, and the needle should be inserted into the longitudinal sinus before that into the donor's vein. No anaesthetic is required, and it is rather an advantage if the child cries when it feels the prick of the needle, as the pressure in the longitudinal sinus will be increased. After the first prick of the needle the child generally remains quite passive.

The point of the needle should be pushed through the/

the skin in the sagittal plane opposite the posterior angle of the fontanelle, the needle being held at an angle of  $50^{\circ}$  to  $60^{\circ}$ . It is usually possible to feel when the point has entered the sinus, and, unless the pressure is negative, blood will flow in drops from the end of the needle. In cases where the pressure is low, no blood may appear, and it is therefore advisable to have the needle attached by a short rubber tube to a syringe containing some saline. Should blood not appear in the barrel of the syringe, when it is believed that the needle has penetrated the sinus, slight suction should be applied. When it has been satisfactorily demonstrated that the point of the needle is resting in the sinus, the adjustable sleeve should be slipped down to the level of the scalp, and fixed. In the meantime, blood should be withdrawn from the donor's vein, and, till the first syringe is ready, a few cc. of saline should be slowly injected into the sinus to prevent the blood clotting in the needle. In this way 50 cc. to 100 cc. or more can be safely given to young infants.

If for any reason citrated blood has to be injected, this can best be done through a needle fitted to the syringe with a two-way stop-cock, such as the writer<sup>31</sup> described for the intravenous injection of eusol.

If/



If reasonable care is taken, there is no risk involved in injecting into the longitudinal sinus fluids used for therapeutic purposes, with the exception of Salvarsan. In cases where the longitudinal sinus is small, the needle may go right through it, and may puncture the cerebral cortex without doing harm. It is only necessary to be sure that the needle is in the sinus before the fluid is injected.

Transfusion from vein to vein with syringe canula apparatus and two-way stop-cock.

This method of transfusion was used on ten occasions. Its object is to provide a means of transfusing from vein to vein without the necessity of using so many syringes as are needed for the simple syringe method. The first instrument of this type which I used is shown in Fig. 16. It was first employed in November 1916, and has proved satisfactory. But, although the principle has been retained, several subsequent modifications of the apparatus have been made.

I. Description of instrument. No.1. Fig. 16.

The canula consists of a flexible U-shaped silver tube with an external diameter/

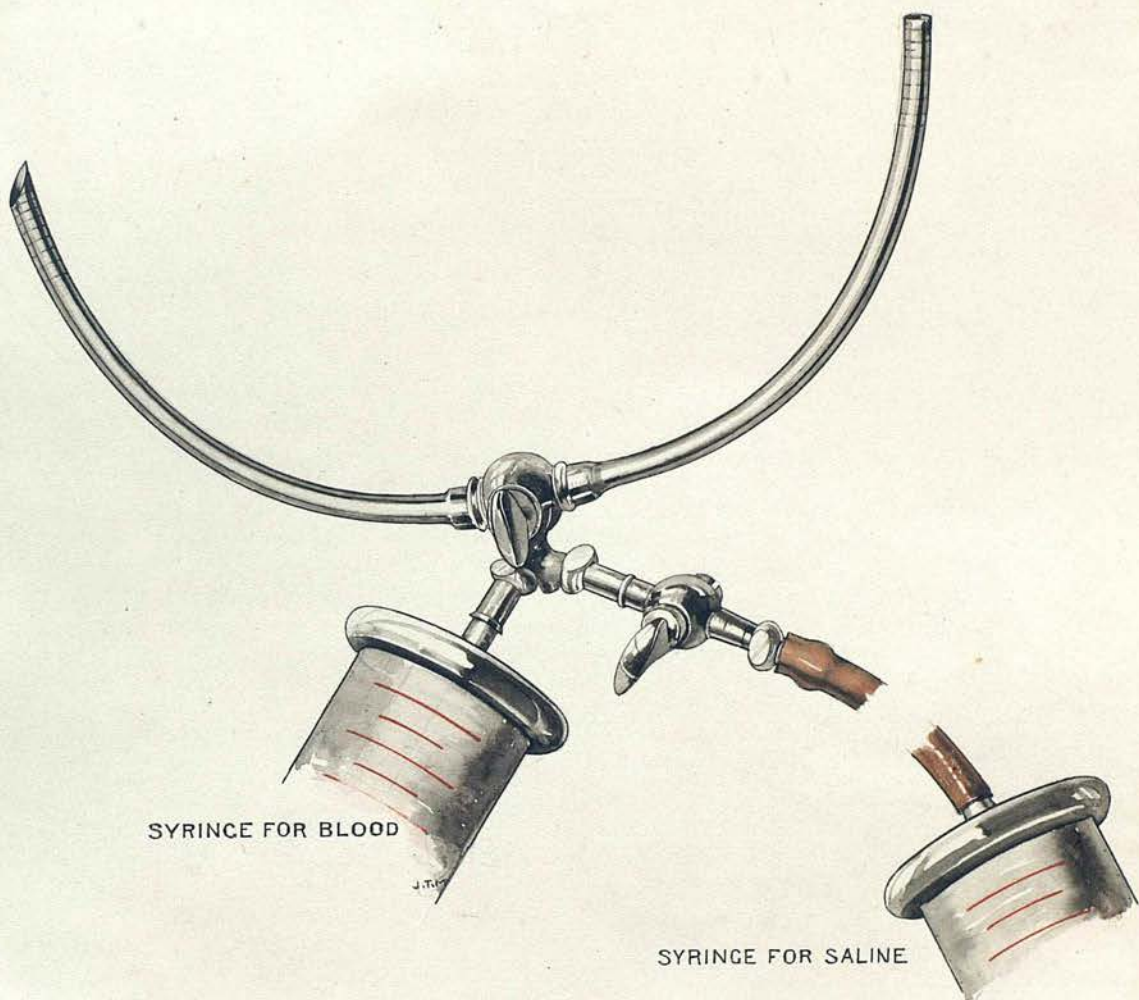


Fig. 16. Transfusion from vein to vein with syringe canula apparatus and two-way stopcock. First instrument used.

diameter of 4 mm. The tips of the canula are about 12 cm. (5 inches) apart, but the distance can be altered by bending the tubes. The limbs of the canula are united by a two-way stop-cock, the lumen of which can be made to connect alternately with one or the other, by rotating the tap of the stop-cock through a right angle. A suitable fitting for the nozzle of a Record syringe is placed at right angles to the U-shaped tube, through the centre of the stop-cock, and a side tube with stop-cock is also provided for injection of saline from a second syringe.

The donor's end of the canula should not be bevelled, as suction is then less liable to press the wall of the vein against the opening. An additional reason for keeping the donor's end of the canula blunt is that in suitable cases the end of the canula can be connected to a special needle inserted through the skin, thus saving an incision.

II. Technique of operation. The canula and syringes are lubricated with liquid paraffin. The donor and recipient are placed recumbent with the arms in a convenient position. It is more reliable to tie the canula into both vessels. In this case the donor's end of the canula should be directed peripherally in the vein. The blood can then be transfused/



transfused without risk of failure. The use of the needle canula, without incision to expose the donor's vein may cause difficulty during the transfusion, if for any reason the point of the needle is dislodged. The clip attachment for the needle-canula previously described practically eliminates this risk.

III. Position of patients. The donor and patient should be placed on parallel tables, but lying in opposite directions, with the left arms held at right angles, so that the elbows are opposite each other. The donor's arm is congested with a tourniquet.

The selected veins are exposed for a short distance under local anaesthesia, and ligated, proximally in the case of the donor, and distally in the case of the recipient. The veins are then lightly clamped, opened and washed out with saline and liquid paraffin, and the end of the donor's canula is inserted and fixed in position. For the better fixation of the canula, the special clamp forceps described for direct transfusion is used. The stop-cock is now turned so as to connect the donor's end of the canula with the fitting for the transfusion syringe, and the clamp controlling the donor's vein is then removed. When the blood has passed through the stop-cock, the transfusion syringe is connected and filled/



filled with blood. The tap of the stop-cock is now rotated, and the recipient's half of the canula is filled with blood from the syringe, and then inserted into the vein, where it is fixed with the clamp forceps. This takes only a moment, and excludes the risk of injecting any air. After the recipient's end of the canula has been inserted and fixed within the vein, the light clamp controlling the vein is removed, and a syringe of blood is injected. By alternately turning the tap of the stop-cock, the syringe can be filled from the donor's vein and emptied into the vein of the recipient. I have transfused with this method up to 900 cc. of blood without any difficulty from clotting, to prevent which various steps have been taken. Unger has succeeded in transfusing large quantities of blood with a single syringe, without detaching the syringe, by spraying the barrel with ether during the transfusion. I found that there is no tendency to clotting if two syringes are kept ready, and used in turn about once a minute. At the same time it is advisable occasionally to inject a little saline in order to keep the stop-cock clear.

Description of instrument No.2. (Fig. 17. )

Although the original instrument described above proved to act well, the rotation of/

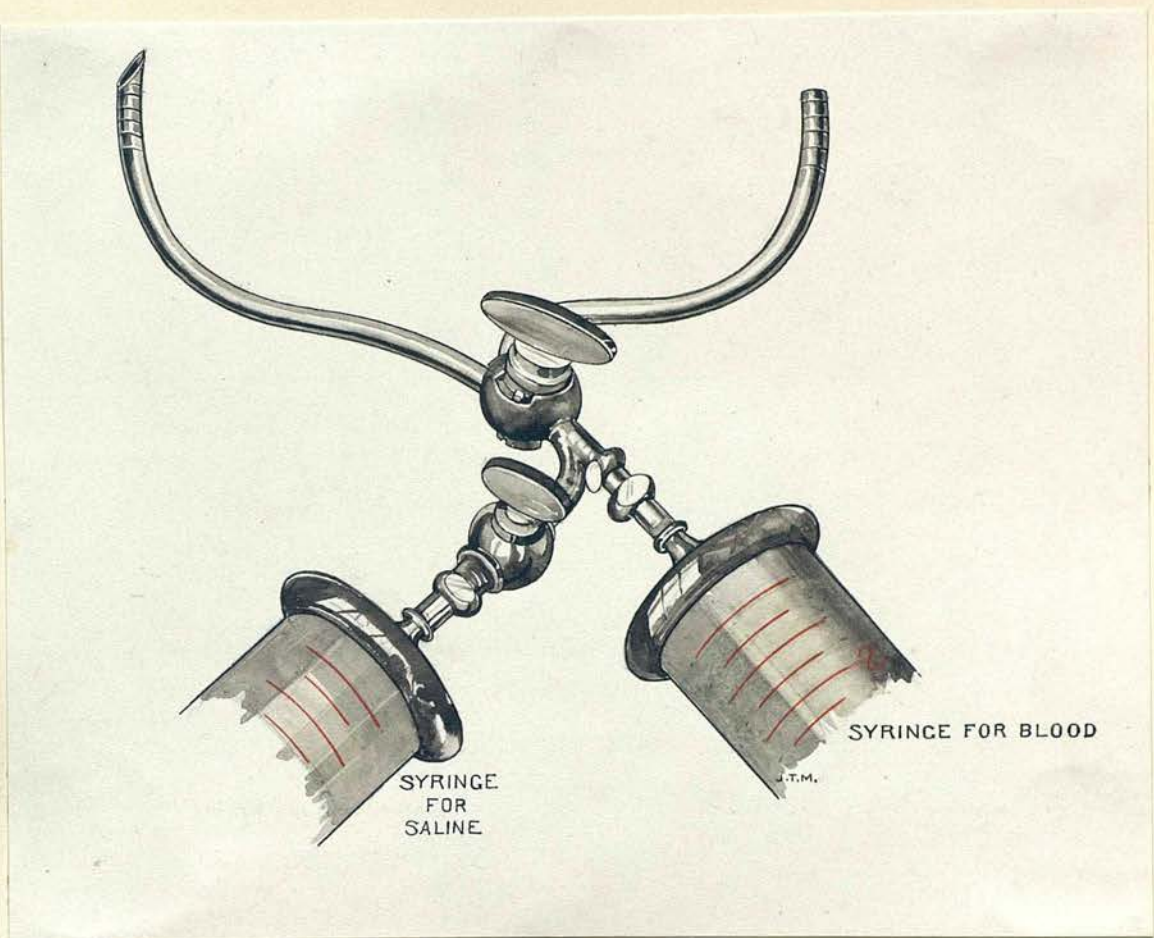


Fig. 17. Syringe-Canula apparatus with two-way stopcock. Second and improved pattern.

of the tap of the stop-cock through a right angle proved awkward, and the instrument was therefore modified.

The stop-cock is 8.5 mm. at its widest part, and its lumen is Y-shaped on horizontal section. The apertures of the divergent limbs are only 3 mm. apart, and moreover the blood stream has not a right angle to negotiate, but an obtuse angle of  $150^{\circ}$ . It was found in practice that the more limited range through which the tap had to be turned made it easier to work. In other particulars the details and method of using this instrument were similar to the first type.

Description of instrument No.3. In order still further to simplify the manipulations and limit the assistance required, further modifications were introduced in a third form of two-way canula. When the first two types were being used, the surgeon required both hands for working the syringe, while an assistant turned the tap of the stop-cock. It sometimes happened that this was not done at the correct moment. As it would therefore be better for the operator to control the combined action of the syringe and stop-cock, the instrument shown in Fig. (18.) was devised. The stop-cock in instrument 3 is on the same principle as that of instrument 2, but is/



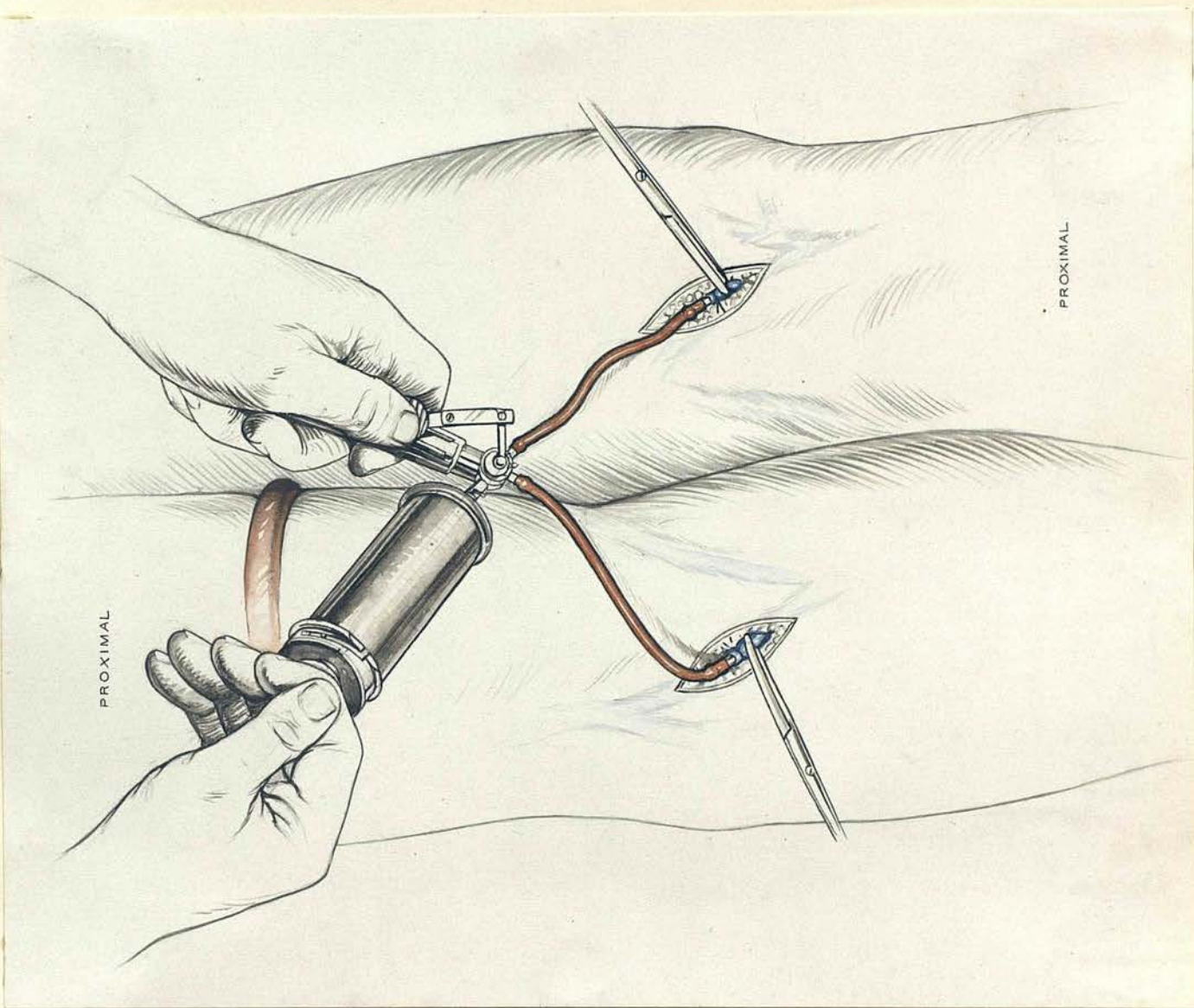


Fig. 18. Syringe-Canula apparatus with two-way stopcock. Third pattern. This form was finally adopted; the details are given in the text.



is 13 mm. in diameter. Instead of the metal limbs of the canulae of previous types, provision was made for connecting the stop-cock to the two canulae in the veins by suitable pieces of rubber tubing. A further improvement in this instrument was made by altering the method of attachment of the syringe to the stop-cock, by the provision of a lock for the nozzle of the syringe, the side tube for the transfusion syringe being grooved to receive a small pin fixed on to the nozzle. A Record syringe can easily be adapted in this way. After inserting the nozzle into the socket, the pin is made to lock by slight rotation of the syringe. A metal handle is attached to the stop-cock, so that the apparatus can be comfortably held and steadied with the left hand. The handle carries a sliding thumb piece operating a hinged lever, which controls the movements of the tap on the stop-cock. The slide has a movement of only 20 mm.

In practice the operator can conduct the transfusion without assistance in manipulating the instrument. The piston of the syringe is worked with the right hand, and the tap of the stop-cock is rotated by moving the slide upwards or downwards with the thumb of the left hand. The stop-cock is made in two pieces, and these, together with the spring lever, can be easily detached for cleaning.

Comment; /

Comment:- The chief theoretical objection to all the methods of transfusing by means of a syringe and canula with two-way stop-cock, is the large amount of surface with which the blood comes in contact outside the body. Unger, however, and others, have found that this objection is more theoretical than practical, and my own experience confirms the good results which others have obtained, with similar forms of apparatus. There has been no clotting in the instrument in any of my cases, although it is almost impossible to imagine that the blood can remain absolutely unaltered. The blood in the syringe and canula is kept in almost constant movement, and this is the principal reason why clotting does not occur. I think it can be safely said that the practical value of the method has been established, and it is certainly one of the quickest methods of performing transfusion.

As compared with the citrate of soda method, the syringe and canula method is quicker, when the time taken to prepare, as well as to inject, the citrated blood is considered. If the citrated blood is already prepared, it can of course be injected more quickly than by any other method.

Transfusion/

Transfusion with citrated blood.

This method has been used on eight occasions. Although elaborate methods for collecting and mixing the blood with citrate of soda have been recommended, I have found in civil practice that the simplest methods were perfectly satisfactory. A series of observations were made in order to confirm the statements made by Lewisohn regarding the anticoagulant effects on blood of various strengths of solutions of sodium citrate.

10 cc. of my own blood were withdrawn into clean, sterile test-tubes containing 1 cc. of varying strengths of sodium citrate solution, and the coagulation time was noted in each case. In the control tube, the blood clotted in two minutes. Citrate in the strength of .05%, .1%, and .15% delayed clotting from 12 to 15 minutes.

This experiment was repeated with blood from another individual, and a precisely similar result was obtained. In the control tube, the blood clotted in four minutes. Citrate in the strength of .05%, .1% and .15% delayed clotting from ten to twenty-three minutes. Blood containing .2% of sodium citrate remained fluid for several days.

These facts confirm the observations that blood is not prevented from clotting by a weaker solution of/  
of/

of sodium citrate than .2%, but they are at variance with the statement that weaker solutions do not at all delay the coagulation time of the blood. It was found that the weaker solutions, while not preventing clotting, delayed it for a few minutes in proportion to their strength.

It is advisable to provide for a slightly stronger mixture than .2% in actual practice, to obviate the risks of error in measuring the amount of blood when it is mixed with the citrate solution. In clinical cases I used sodium citrate with blood in the proportion of .25%, to provide for any margin of error. The slight excess of citrate used is negligible as a toxic factor.

Withdrawal and preparation of the blood.

The donor's arm is congested with a tourniquet, and the largest available vein is selected. A hollow needle and canula, similar to the needle canula described under the syringe method of transfusion and prepared by lubricating with liquid paraffin, is inserted proximally into the donor's vein. The hollow needle is then withdrawn, leaving the canula clipped in place. The blood is allowed to flow directly into a suitable wide mouthed graduated flask, to which has been previously added 25 cc. of/



of a 2.5% solution of sodium citrate. If a suitable flask is not available, the blood may need to be directed by means of a tube to prevent it from coming into contact with the sides of the flask, and a piece of glass tubing with a short rubber tube to connect it to the canula is required. When the 250 cc. mark is reached, another 25 cc. of citrate solution is added, and this proportion is maintained till the desired amount is reached. In transfusions of 500 cc., I found no difficulty in getting the amount of blood from the donor's vein by the increased pressure from the tourniquet, but in amounts larger than this, it may be necessary, in order to draw off the blood quickly enough to avoid premature clotting in the needle, to use an aspirating bottle, provided also with an inlet tube for addition of citrate. It is necessary to stir the blood gently with a glass rod to ensure thorough mixing, but it is unnecessary to strain it as is done with defibrinated blood.

Injection of the blood. The simplest method is to allow the blood to flow by gravity through the funnel, tubing, and canula, used for the infusion of normal saline. After the collection of the blood, and during its transfusion, the flask should be kept in a basin of water slightly above blood heat.

Comments./

Comments. The great advantage of the citrate of sodium method over all other methods is its simplicity. The extensive use of this method in France has disproved the theoretical objections to the use of an anticoagulant, at least in cases of primary haemorrhage and shock. The fact that citrated blood can be kept for some hours at least is an enormous advantage, and it can if necessary be preserved for several days by the methods of Rous and Turner. It must also be considered as an advantage that with citrate of sodium the donor need not come in contact with the patient, and that the blood can if necessary be transported. The experimental and clinical work which has been done on the preservation of corpuscles in citrate, dextrose, and gelatin solutions has proved that citrate has no injurious effect upon the life of the corpuscles within a reasonable time. In cases of primary haemorrhage which I treated with citrated blood there was every indication that the corpuscles continued to live and to function after being transplanted.

Although citrate does not appear to affect the corpuscles, reactions in the form of a rigor and elevation of temperature are more frequently experienced than when unmodified blood is transfused.

I was able to compare the effects of citrated and whole blood in a case of pernicious anaemia.

The/

The patient was transfused twice from the same donor, whose blood was known to be compatible. A similar amount of blood was injected on each occasion (450 cc). The subsequent progress of the case and the blood counts showed that the citrated blood failed to produce any continued benefit and that the corpuscles were destroyed within a few days; When whole blood was transfused later by the syringe and U-shaped canula method the transplanted corpuscles were maintained intact and a fresh remission of the symptoms was initiated.

It is probable therefore that citrated blood, while perfectly successful in cases of haemorrhage, is not so effective in diseases of the blood. One of the methods of whole blood transfusion should be preferred in cases of Pernicious anaemia, Purpura or the secondary anaemias, when the operation is indicated.

#### CONCLUSIONS/

CONCLUSIONS AS TO CHOICE OF METHOD.I. Direct transfusion.

- (a) It reduces the chances of thrombosis and embolism to a minimum.
- (b) The operation is more difficult to perform than indirect transfusion.
- (c) The use of the radial artery is a greater sacrifice for the donor than a vein.
- (d) The radial artery is occasionally too small for the purpose.
- (e) The amount of blood cannot be exactly measured.

II. Indirect transfusion.A. The use of syringes and canulae, with or without two-way stop-cock.

- (a) The operation is simpler than direct transfusion.
- (b) The method demands less sacrifice from the donor.
- (c) The operation can be more quickly performed than direct transfusion, or any other method.
- (d) The amount of blood transfused is known.
- (e) The risks of clotting in the apparatus can be obviated.
- (f) Simple instruments can be improvised for the syringe method.
- (g) The patient and donor must be brought into contact.



B. Citrate method.

- (a) Sodium citrate mixed with blood in the proportion of .25% maintains the blood fluid for several days..
- (b) Citrated blood can be safely used several hours after preparation.
- (c) The withdrawal and preparation of blood for transfusion is simple..
- (d) An incision is not required to expose the donor's vein.
- (e) There is more tendency to reaction than after transfusion with unmodified blood.
- (f) When a reaction occurs, it does not affect the patient seriously.
- (g) Large quantities of blood can be transfused without fear of toxic action on the part of the citrate..
- (h) Results in shock and primary haemorrhage are as satisfactory as with unmodified blood.
- (i) The coagulation time of the blood is temporarily shortened after transfusion with citrated blood.
- (j) There is no risk of increasing the tendency to haemorrhage after the use of citrate of sodium.
- (k) Unmodified blood should be preferred to the citrate of sodium method in pernicious anaemia and other diseases of the blood.

With the different methods of performing direct and indirect transfusion which I have used, almost equally good results technically may be obtained. I observed no practical difference in the results with arterial or venous blood. Transfusion from vein to vein is on the whole more simple, and can be more quickly performed than direct transfusion; and is therefore the method of election for transfusion of unmodified blood. As already mentioned, the operation of vein to vein transfusion can be satisfactorily done with more than one form of apparatus. It is sufficient for the operator to be familiar with one method.

As the results of transfusion with the citrate method in cases of haemorrhage and shock are as good as after transfusion with unmodified blood, this method should be selected as the routine procedure under these conditions.

RISKS OF TRANSFUSION.

I. Sepsis. With modern operative technique, the risks of sepsis are almost eliminated, and I have not come across a recent case in which serious infection has followed transfusion. Sepsis has been absent in the cases I have observed.

II. Air embolism. With any of the modern methods of transfusion, there is practically no opportunity for air to enter the patient's veins. I have injected 15 cc. of air with a syringe intravenously in a dog weighing 8.25 kilos. without ill effects. The rapid suction of air through a wound of a large vessel of the neck is much more apt to embarrass the heart than a small amount slowly injected into a peripheral vein, and it is safe to say that the risks of air embolism in transfusion, as it can now be done, are negligible.

III. Overtransfusion. If the volume of the blood is too rapidly or too much increased, the right side of the heart will become dilated, and the patient will complain of discomfort. In young and healthy patients, who are transfused because of haemorrhage, there is little risk of overdistention of the heart and vessels. It is more likely to occur in cases of pernicious anaemia, or of secondary anaemia, conditions which are commonly associated/

associated with degeneration of the myocardium. It is important therefore in these cases to have some idea of the amount of blood which should be injected, and even with moderate amounts the rate of injection must be carefully regulated. I observed the symptoms of over transfusion in one of my cases. The patient was suffering from pernicious anaemia, and was profoundly anaemic. The red corpuscles numbered 600,000, and the haemoglobin was 18%. There were haemic murmurs in all areas, her pulse varied from 100 to 112 per minute, and she was extremely weak. The blood pressure was 106 mm. Blood was transfused directly from the radial artery of her husband, and at the conclusion the blood pressure was raised to 130 mm., and the number of corpuscles per cc., and the haemoglobin per centage were doubled. Towards the close of the operation, the patient became somewhat breathless, and complained of oppression in the chest. Her lips were cyanosed, the pulse was slightly irregular, and she had a tendency to cough. The symptoms however passed off quickly, and it was noted in the case that the patient felt much better after the transfusion. Her subsequent progress was satisfactory.

As an explanation of the overtransfusion in this case it is interesting to note that the donor was/



was of a much heavier build than the patient, and that the blood was received directly into the external jugular vein. . Boycott and Douglas have shown experimentally that, when the total haemoglobin of a normal rabbit is increased by about one-third by overtransfusion, the amount of haemoglobin in the blood again returns to its normal level in from eight to fourteen days. In the case referred to above, the haemoglobin was reduced eight days after transfusion from 36% to 25%, but thereafter steadily improved.

Cases in which serious symptoms are caused by overtransfusion of blood are exceptional, and with reasonable precautions this complication may be avoided.

#### IV. Intravascular thrombosis and embolism.

The risks from formation and detachment of a clot in the form of an embolus during a transfusion, or of gross thrombosis in the vessels afterwards seems to be greatly exaggerated, and there are very few references, in recent literature, to their occurrence. The fact is that any clots which occur in connection with the instruments towards the conclusion of a transfusion are firmly adherent, and do not tend to become detached or free in the recipient's/

recipient's vein. I have frequently seen clotting in the canulae towards the end of a protracted transfusion, and have always found that the clots were firm, and difficult to remove from the tubes. None of my cases presented any symptoms of thrombosis or embolism. The more frequent occurrence of intravascular thrombosis and embolism in earlier times was probably due to the injection of blood already undergoing the early stages of coagulation.

V. Dangers from incompatibility of blood.

It is now recognised that the blood of one individual may be toxic to that of another of the same species, independent of any error in the technique of transfusion. As recorded in the historical note, the risks from transfusion between individuals of different species were long suspected. The occurrence of haematuria, and of other alarming symptoms, was also not infrequently observed in cases of transfusion between human individuals, but it was not till Bordet finally demonstrated the action of haemolysins that a means was offered for diminishing the risk of haemolysis after transfusion by preliminary testing of the bloods.

Haemolysis was recognised as a possible source of danger, prior to 1908, but in that year, Landsteiner,<sup>32</sup> pointed out that agglutination of corpuscles//

corpuscles could occur from the mixing of normal bloods. He definitely established that iso-agglutinins were normally present in human blood, and went so far as to divide human sera into three groups, a classification which was completed in 1910 by Moss,<sup>19</sup> who added a fourth group.

Hektoen<sup>33</sup> later confirmed Landsteiner's observations, and suggested further that the occurrence of iso-agglutinins in human blood might prove a source of danger in cases of transfusion.

Agglutination and haemolysis are therefore two of the obvious dangers which may be incurred by transfusion between individuals of the same species. According to Hektoen,<sup>33</sup> agglutinins and haemolysins occur much less frequently in animals than in man, and he was not able to find them in the serum of rabbits, guinea pigs, dogs, horses, or cattle.

Moss states that iso-agglutinins occur in the serum of about 90%, and iso-haemolysins of about 25%, of adult human beings, and that these proportions do not vary in health or disease. From his studies of iso-agglutinins, Moss found that human sera could be divided into four groups, and by repeated examinations, he further established that the group of an individual remained constant. These observations have been subsequently confirmed, and Brem,<sup>34</sup> writing in/

in 1916; stated that he and his co-workers had found the work of Moss so accurate that during six years they had never found any errors in his observations, and had been able to add nothing essential to them.

Although Moss was unable to classify individuals according to the isolytic action of their blood, he established a relationship between the iso-agglutinins and the iso-haemolysins. Agglutination frequently occurs independently of haemolysis, but the latter hardly ever occurs unless preceded or accompanied by the former; and it can be simply stated therefore that if there is no agglutination between the respective sera and corpuscles of the donor and recipient, there will be no risk of haemolysis after transfusion.

Moss's classification of human sera.

Group I. (10%)

Serum agglutinates no corpuscles.

Corpuscles agglutinated by sera of

Groups II, III, and IV.

Group II. (40%).

Serum agglutinates corpuscles of Groups

I and III.

Corpuscles agglutinated by sera of Groups

III and IV.

Group III./



Group III. (7%).

Serum agglutinates corpuscles of Groups  
I and II.

Corpuscles agglutinated by sera of Groups  
II and IV.

Group IV. (43%).

Serum agglutinates corpuscles of Groups  
I, II, and III.

Corpuscles agglutinated by no sera.

No agglutination or haemolysis occurs between the sera and corpuscles of individuals of the same group, and it is therefore possible to select a donor whose blood will be compatible with that of the recipient. Although it is desirable to have a donor in the same group as the recipient, experience has shown that there is no risk of agglutination occurring if a donor is chosen whose corpuscles are not agglutinated by the serum of the recipient.

Agglutination and haemolysis of the recipient's blood by the serum of the donor's blood are prevented by the dilution of the blood of the donor when mixed with the comparatively large amount of the blood of the recipient.

It will thus be seen that:-

A group I recipient may receive blood from Groups

I, II, III and IV.

" " II " " " " Groups II and IV.

" " III " " " " " III and IV.

" " IV " " " " " IV.

The preliminary tests for selecting a donor may be made in either of two ways.-

- A. The donor's and recipient's blood may be tested for mutual agglutination.
- B. The donor's and recipient's corpuscles or sera may be tested against known sera or corpuscles to determine the group to which each belongs.

A. Test for mutual agglutination.

It is desired to ascertain whether agglutination occurs between the serum of either individual and the corpuscles of the other. The method which I have used is the following. A specimen of serum is obtained from each individual by collecting 1 or 2 cc. of blood in a sterile test-tube. The serum is pipetted off, after allowing the clot to contract, or after centrifuging. A suspension of both donor's and recipient's corpuscles is made by mixing two or three drops of blood in 1 cc. of a 2% solution of sodium citrate. Hanging drop preparations are then made by mixing.-

- I. The donor's serum with the recipient's corpuscles.
  - II. The recipient's serum with the donor's corpuscles.
- in the proportion of one platinum loopful of corpuscles to two of serum. The corpuscles and serum are uniformly mixed with the loop of the needle, and the slides/

slides are examined under the microscope. If agglutination is going to occur, it should be apparent in a few minutes. If the patient's serum does not agglutinate the donor's corpuscles, the latter may be safely used for transfusion, and further if there is no agglutination of the patient's corpuscles by the donor's serum, both belong to the same group, and their bloods are compatible. Lee,<sup>35</sup> considers that in selecting a donor the minimum procedure should consist of establishing the fact that the patient's serum does not agglutinate the donor's cells, and states that in case the test is negative it is advisable to raise the coverglass, making sure that the serum and cells are well mixed, and to examine the preparation a second time.

The clumping of corpuscles resulting from agglutination in hanging drop preparations can be observed macroscopically as well as microscopically, and it is not difficult to distinguish agglutination from rouleaux formation. The value of this method lies in the fact that agglutination cannot be interfered with by too rapid haemolysis, owing to the presence of antihaemolysin in the citrated blood.

B. Test for determining the group to which an individual belongs.

Without a direct test between specimens of the donor's and a recipient's blood, it is possible by ascertaining/

ascertaining the groups to which they belong to know whether they are compatible or not. Whenever possible, it is advisable to have at hand donors whose blood group is known. In order to determine the group of an individual, it is necessary to have standard sera of known groups II and III.

According to Moss,<sup>36</sup> the agglutinating reactions of standard sera will remain unaltered in sealed glass tubes for six months, if they have been prepared with aseptic precautions, and kept in the dark. Sufficient serum can be collected from 5 cc. of blood to provide for several tests, and it is convenient to have the sera of groups II and III preserved in sterile capillary pipettes, the ends of which are sealed.

"The determination of the group of any individual is easily and quickly carried out. A single drop of blood from the finger-tip or ear is allowed to fall into a test-tube containing 8 cc. - 10 cc. of physiologic sodium chloride solution. The tube is shaken or rotated in order to obtain a uniform suspension. On each of two cover slips a very small drop of the corpuscle suspension is placed by means of a capillary pipette or platinum loop: to one, a drop of group II serum is added, and to the other, a drop of group III serum. The serum and the corpuscles are/



are mixed on each cover slip, inverted over a hollow ground slide, and examined under the microscope.

Agglutination may take place in a few minutes at room temperature, but it is a safe rule to allow half an hour at  $37^{\circ}$  C. to elapse before concluding that there is no agglutination." (Moss<sup>36</sup>).

The following table shows how this determination is carried out:-

Unknown Corpuscles	Serum of		Group to which corpuscles belong.
	Group II	Group III	
X	+	+	I.
X	0	+	II.
X	+	0	III.
X	0	0	IV

+ --- Agglutination.

0 --- No agglutination.

Tests may be carried out in a similar way by using unknown serum against the known corpuscles of groups II, and III; but as corpuscles do not keep long, it is simpler to use standard sera.

The occurrence of agglutination is much less dangerous than that of haemolysis. According to Ottenberg and Kaliski<sup>37</sup> human isoagglutinins are present only in weak concentration, and are generally not active in greater dilution of the blood than 1 in 10, or 1 in 20. The conditions are more favourable/

favourable for agglutination when the patient's serum is agglutinative to the donor's cells, but it is probable that massive clumps of cells form only in exceptional cases. Ottenberg and Kaliski describe three cases followed by serious symptoms in which the patient's serum was agglutinative to the donor's corpuscles, and in two of these cases they observed phagocytosis of the red blood corpuscles. In both cases phagocytosis of the red blood corpuscles was seen in films made at the end of the transfusion: the first patient died in forty-two hours without symptoms of haematuria, the second within eight hours. In the third case mentioned, films were not examined for phagocytosis, but the patient developed intense haematuria. These cases suggest a toxic action of the patient's serum on the donor's corpuscles, which were destroyed, and virtually changed into foreign bodies. Practically all observers are agreed that agglutination per se is an exceptional cause of toxic symptoms, and that serious reactions from incompatibility of blood after transfusion are rare unless haemolysis has occurred. It is possible that this may be explained by the masking of agglutination by the coincident haemolytic action of the serum on the corpuscles.

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According to Bernheim, haemolysis is the only real danger of transfusion. The occurrence of haemoglobinuria/

haemoglobinuria is not so frequent as might be supposed, although there is no reason to doubt that considerable haemolysis may occur, without the appearance of haemoglobin in the urine. Bernheim quotes statistics of eight hundred cases of transfusion, many of which were done without preliminary tests. Haemoglobinuria occurred in fifteen cases, (roughly 2%), with four deaths and eleven recoveries.

While many cases of transfusion with incompatible blood have been successfully performed with benefit to the patient, and without haemolysis or serious reaction of any kind, presumably owing to the varying strength of the haemolysins, it is impossible, unless preliminary tests have been made, to exclude the occurrence of haemolysis with possible fatal results. Haemolysis with a serious reaction may follow transfusion from a donor, whose blood has been found by testing to be apparently compatible. There is always the possibility of error in laboratory tests. Lindeman<sup>39</sup> records that, in his first series of one hundred and fifty transfusions, 35% of the patients had a feverish reaction, and three cases suffered from haemolysis. In a subsequent series of one hundred and fifty-five transfusions, in which, with a few exceptions, the preliminary test had been supervised by himself, no instance of haemolysis occurred, and there were no deaths attributable to the transfusions.

GROUP REACTIONS.

According to Brem,<sup>34</sup> reactions due to incompatibility of the bloods come on quickly as a rule; only 10 cc. of blood are sufficient to cause serious symptoms. In extreme cases the symptoms may resemble those of anaphylactic shock. There is a feeling of fullness in the head, suffusion of the face and eyes, precordial distress, dyspnoea, coughing, back, ache, rapid and small pulse, which may become imperceptible at the wrist, and sometimes complete loss of consciousness and convulsions. Should the patient recover from the initial acute symptoms, haemoglobin is likely to appear in the urine. When haemolysis is slighter in degree, the chief manifestations of the phenomenon are the occurrence of chill, vomiting, and fever. Haemoglobinuria may be absent, and the signs of the destruction of the red corpuscles may be indicated only by an increase of haemoporphyrin in the urine. The immediate effects of transfusion with incompatible blood cannot be predicted, even when it is evident that haemolysis has occurred. A few cases have been recorded in which the patient has died with acute toxic symptoms during the transfusion. In other cases the haemolysis may proceed with increasing haemoglobinuria, and finally with/



with partial or complete suppression of urine, and a fatal issue, possibly associated with intravascular thrombosis. In other cases the patient merely passes through a temporary crisis, and recovers, without the object of the operation having been attained.

It is generally accepted that preliminary tests should be carefully carried out before any transfusion is done. If possible, a donor of the same group should be selected, or one whose corpuscles are not agglutinated by the patient's serum. Cases however are bound occasionally to arise, which are so urgent as to preclude the slight delay necessary for testing the blood of the donor. Or, again, it may be impossible to obtain a choice of donor. The question therefore arises in urgent cases whether it is advisable to risk possible incompatibility of the bloods, or to postpone the operation till a suitable donor can be selected. Under these circumstances, each case must be decided upon its own merits; in my own experience, the risks of incompatibility are not so great as to warrant delay in carrying out the transfusion. For some time I omitted all tests before transfusion, partly on these grounds, and partly because Bernheim and other writers had expressed the opinion that the results of the tests in vitro did not correspond to those in vivo.

In/

In my own practice, the need for transfusion was often urgent, and the circumstances of the case frequently precluded the choice of a donor. In many cases, all preliminary preparations for the transfusion had been made by the physician in charge of the case, and I had no opportunity of examining the patient prior to the operation. The modern technique of testing the compatibility of blood has been much simplified by the methods of Moss and Brem, and gives a more accurate result than was obtained with the earlier methods. Since 1917, I have used the agglutination tests whenever possible, either by ascertaining the groups to which the bloods of the donor and recipient belonged, or by testing the bloods directly for agglutination. The following recent case furnishes an example of the innocent effects following transfusion with untested blood. Transfusion was indicated in this case because of the urgent nature of the patient's symptoms, and was successfully performed with a mixture of blood derived from seven donors. The circumstances of the case were as follows.

The patient was a young woman, aetat. 25, suffering from tuberculous disease of the sacro-iliac joint, of several years standing. Her health had been much affected by the presence of discharging sinuses, and the diseased area had been exposed and scraped/

scraped by an open operation. There was much bleeding at the operation, and, subsequently, profuse secondary haemorrhage occurred necessitating ligation of the internal iliac artery. Four days later, a severe haemorrhage again occurred, and the patient, who was previously in a somewhat feeble condition, became completely collapsed. The haemorrhage was controlled with packing, but when I saw the patient two hours later, she was completely blanched, and the pulse was felt with difficulty. She was semi-conscious, and the systolic blood pressure was between 50 mm. and 60 mm. Her condition was obviously hopeless, and transfusion offered the only chance of prolonging her life. As no relations or other likely donors were at hand, it was decided to ask a student to volunteer as donor. It was not considered desirable to take the necessary amount of blood from any of those who volunteered, as the individuals were either not sufficiently fit to justify the loss of more than a small amount of blood, or were doing responsible work as members of the staff, and could not therefore be readily spared on account of temporary indisposition, or were sitting for their final examination two days later. The only justifiable means of obtaining the blood seemed to be to collect it from several individuals, and in view of the patient's hopeless condition, it was decided to risk the/

the many incompatibilities which such a mixture could produce. 600 cc of blood were taken from one nurse, two residents, three students, and the writer.

In performing the transfusion there was therefore a mixture of the blood of eight individuals in the recipient. The blood was withdrawn from the several donors and mixed with sodium citrate. While the blood was being collected, the patient became pulseless, and appeared to be sinking, and it was a question whether the preparations for the transfusion could be completed before the patient died. A superficial vein was exposed ready for the transfusion, while the blood was being obtained. There was no bleeding from the tissues, and on opening the vein, only a few drops of blood escaped.

After a third of the blood had been introduced, a faint colour appeared in the patient's finger-nails, and the pulse became palpable. When half the solution had been given, the patient's breathing became somewhat rapid, and the rate of flow was retarded. About fifteen minutes was taken over the entire transfusion. Before the completion, breathing was again quiet, and the patient regained consciousness, and was able to speak and answer questions clearly. At the conclusion of the transfusion, the blood pressure was 90 mm. No reaction of any kind followed, and/



and the patient continued to improve till the fifth day, when a fresh haemorrhage occurred. Several profuse haemorrhages occurred on the following day, and the patient died from exhaustion.

This proves that it is justifiable to transfuse a patient without preliminary tests when the case is urgent.

My own observations are based on forty-six transfusions, and preliminary tests were performed on fourteen occasions. No haemoglobinuria occurred in any of the series of cases, but there was active haemolysis of the transfused corpuscles in one untested case, a patient suffering from pernicious anaemia, as shown by the appearance of jaundice on the third day after transfusion. The patient also had a considerable rise of temperature for a week after the operation, but subsequently returned to his former state. In a considerable number of the untested cases there was a temperature reaction varying from  $99^{\circ}$  to  $101^{\circ}$ , but the patients did not appear to suffer materially from the disturbance. There is no doubt however that reactions were less common in the tested cases.

CHOICE OF DONOR.

(a) In infants. According to Moss and Happ,<sup>30</sup> blood groups are not established before the second year of life. Cherry and Langrock<sup>40</sup> investigated the compatibility of mothers' and infants' blood by testing the bloods of new born babies and their mothers. Thirty-four tests were done with uniform results and no agglutination or hemolysis occurred. The authors concluded that all mothers could be used safely as donors for their infants. Sydenstricker states that it is safe to transfuse infants under two years of age with their mothers' blood, but thinks it advisable to employ preliminary tests even in these cases.

In four cases of transfusion in infants which I record here, the mother acted as donor in one case, the father in another, and the Sister in charge of the children's ward of the Deaconess Hospital in the remaining two. Previous agglutination tests had shown her to be a suitable donor for any case as she belonged to Group 4.

(b) In adults. In the absence of preliminary tests a relation is the most suitable donor. Provided that the bloods are compatible the question of relationship is not important. Lindeman found that reactions were more frequent/

frequent after transfusions, in which preliminary tests had shown compatibility of the bloods, when the donor was a stranger than when he was related to the recipient. It has been suggested that the blood Groups depend upon the Mendelian Law and, if this should be proved correct, it may explain why relations are more likely to belong to the same Group.

As has been previously stated the donor may be considered suitable for transfusion either if he belongs to the same Group as the recipient or if his corpuscles are not agglutinated by the recipient's serum.

As corpuscles of Group 4 are not agglutinated by the serum of any other Group, individuals of this Group can be regarded as universal donors.

Young adult males naturally make the best donors. In the case of females the superficial veins may be invisible and thus require an incision, and I have found the radial artery also sometimes to be small for the purpose of direct transfusion.

The risks to the donor are not great if reasonable care is taken, but the following extract from the Daily Sketch of 21st October, 1918, shows that this is not always the case:- "A transfusion of blood being necessary to save the life of Pte. Girling, patient at Queen's Hospital, Sidcup, his brother Leonard,/"

Leonard, employed at Woolwich Arsenal, offered himself. The operation was successful and the soldier is recovering - but the brother has died as the result of his sacrifice".

Apart from possible infection in certain septic cases, where the patient and donor come in contact, the chief risk which the donor runs is from the rapid withdrawal of a large amount of blood. In my cases of indirect transfusion where the amount of blood has been measured, and varying totals up to 900 ccs. of blood have been transfused, the donor has in no case showed the effects of the loss of blood except possibly by a slight pallor and weakness. In two of the cases of direct transfusion, in which the volume of blood could not be estimated, the donors fainted and required prompt treatment to restore them. From the general impression obtained from the effects upon the donor I am inclined to think that on the whole - a greater amount of blood is transfused with the direct method than in the average case of indirect transfusion.

None of the donors in this series have suffered more than temporary indisposition and they have all been perfectly fit within a few days at most.

When there is time it is as well to exclude syphilis in the donor by the Wasserman test. Bernheim records that a patient has been infected with malaria by a transfusion.



OBSERVATIONS ON THE EFFECTS OF THE TRANSFUSION  
OF BLOOD ON EXSANGUINATED PATIENTS.

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The immediate beneficial effects of transfusion of blood on patients suffering from profound anaemia are often remarkable, but they may be modified to a considerable extent by the presence of symptoms due to slight degrees of incompatibility or to overdistension of the right side of the heart. In a case where the technique is in every way satisfactory the following signs of improvement may be noted:-

(1) Colour. The first result of transfusion is the appearance of colour in the patient's face; this may take the form of a slight capillary flush, but sometimes, before any diffuse colour appears, small venules in the skin become noticeable.

The improvement in colour usually appears first in the lobe of the ear or on the cheeks, especially in the malar region; but it often appears simultaneously on the nose; or in the mucous membrane; and is usually noticed about five minutes after the transfusion has commenced. At first scarcely perceptible the fresh colour in the patient's complexion soon becomes obvious, and the pallid or waxy skin may finally assume a healthy pink colour; but this of course will depend upon the amount of blood trans-/-

transfused. The rapid change of complexion from complete pallor to a healthy colour is often most striking, and, in addition, the lemon yellow tinge characteristic of pernicious anaemia may completely disappear. At the conclusion of the operation the patient's colour frequently suggests a richer blood than is shown by the hemoglobin count, and the improvement in colour may be less pronounced a few hours later.

As the colour improves the face seems to fill out, losing its pinched and sunken look, and at the end of the operation it is not unusual for the appearance of the donor to suffer in contrast with that of the patient.

(2) Mental. Nothing can be more dramatic than the effect of transfusion on the patient's cerebral functions, especially when he is unconscious at the commencement of the transfusion. My cases have often been lifted on to the operating table in a more or less comatose condition, and have awakened during the transfusion to a knowledge of what was going on. Even as small an amount of fresh blood as 200 cc. may suffice to restore consciousness. With returning consciousness the patient takes an interest in the proceedings and soon begins to understand and answer questions. Occasionally such cases take/

take a lively part in the conversation and actually appear exhilarated. One of my patients, who was unconscious and moribund before the transfusion, became first conscious and then talkative and bright, remarking among other things that she hoped for the sake of her husband, who was acting as donor, that the operation would be over before 10 o'clock so that he could get his usual refresher!

The circumstances are more dramatic when the patient and donor are in close contact than when the blood is simply introduced through a funnel and tubing, and the patient is ignorant of the nature of the treatment. It is not unusual for the patient to express his gratitude to the donor and to be solicitous of his welfare. An elderly lady who was transfused when in an unconscious state regained consciousness on the table and at first was somewhat embarrassed and indignant at the presence in her bedroom of her chauffeur, who was acting as donor; Before the operation was over, however, she had a clearer perception of the nature of the procedure and suitably expressed her gratitude to the chauffeur for his sacrifice.

Even when the patient is not unconscious, he is usually dull and apathetic and often oblivious to his surroundings. In such cases the improvement in the mental/

mental state is also striking.

The relief of symptoms shows itself in different ways. As a rule the patient states that he feels better and stronger at the conclusion of the transfusion. Various symptoms may be mitigated, such as numbness and tingling of the limbs, and impaired vision; and the annoyance of audible pulsation may be removed. One patient stated that the main difference she noted was a sensation of warmth and comfort, lacking before.

Many semi-conscious patients are restless, and their uncontrolled movements are apt to interfere with the operation. Such movements may be due to air hunger or simply to the fractious or irritable condition of the patient; these cases usually become quiet and placid as the transfusion takes place.

(3) Changes in the Pulse. The pulse is usually rapid and may be either very small or imperceptible at the wrist. In some cases of haemorrhage the pulse rate may be 150 or 160 per minute. The strength of the pulse increases *pari passu* with the improvements in the patient's colour, and as the vessels become filled the heart itself contracts more strongly. It is not unusual for the pulse at the conclusion of the transfusion to be diminished from 150 to 120 per minute. Improvement in the pulse rate is more marked/



marked in cases of profound anaemia from recent haemorrhage than in cases of chronic anaemia. The increasing facility with which blood for haemoglobin estimation can be obtained by pricking the ear is a further sign of the improved condition of the circulation, and, if an operation is in progress during the transfusion, the tissues will be found to bleed more freely in proportion to the amount of blood transfused.

(4) Blood Pressure. A distinct change is noticed in the blood pressure particularly in cases of primary or secondary haemorrhage. In most of the cases requiring transfusion the blood pressure is low, generally below 100 mm. and often 70 mm. or less. The increase of pressure may be as much as from 50 to 60 mm. to 90 or 100 mm. or more; shortly after transfusion the blood pressure may return to the normal level. The combination of a rise in blood pressure and a fall in pulse rate is characteristic of a successful transfusion in cases of haemorrhage. The rise in the blood pressure naturally varies with the amount of blood introduced, and, if an over-transfusion is given, the pressure may rise to a remarkable degree as shown by experimental work.

(5)/

- (5) Respirations. The respirations are apt to be fast and laboured if the patient is suffering from air hunger.

The signs of deficient oxidation gradually diminish or disappear as the donor's corpuscles increase the oxygen-carrying-capacity of the blood. I have seen cases gasping for breath, so much so that it was difficult to keep them still, completely relieved of their respiratory embarrassment during the course of the transfusion, the respirations falling from 50 to 30 per minute.

- (6) Increase in the haemoglobin percentage, and in the Red corpuscles count per cubic millimetre.

Repeated examinations of the haemoglobin were made during transfusion in the great majority of my cases, the only exceptions being certain emergency cases where there was no assistance available.

The average increase in the haemoglobin count, taken from a series of pernicious anaemia cases, which were completely observed, was 19 per cent; The greatest increase noted was in one case where the haemoglobin was raised from 28 to 73 per cent an increase of 45 per cent;

The average increase in red corpuscles in the same cases was about one million per cubic millimetre, so that the haemoglobin and corpuscles were increased by transfusion in the same proportion.

DISCUSSION REGARDING THE VALUE OF TRANSFUSION  
IN CASES OF HAEMORRHAGE

My observations are based on ten cases, full details of which are given in Volume 2; (Cases 1 to 10). The value of transfusion in these cases will be discussed under the following headings:-

- I. Transfusion in cases of Haemorrhage uncomplicated by Shock.
- II. Transfusion in cases of Haemorrhage complicated by Shock.
- III. Transfusion of Cases of Secondary Haemorrhage.
- IV. Effects of Transfusion on Arrest of Haemorrhage.

One of the first effects of haemorrhage is to cause a lowering of blood pressure in proportion to the amount and rate of loss of blood. When the haemorrhage is not immediately fatal and the bleeding is arrested there is a tendency, as the tone of the vessels recovers and the volume of the blood is increased by the body fluids, for the blood pressure gradually to rise again. Death may be due to loss of corpuscles, but may equally well result from continuance of low blood pressure. Bayliss has pointed/

pointed out that a diluted blood at moderate pressure is much more efficient for maintaining the vitality of the tissues and organs than a concentrated blood at low pressure.

It is important, therefore, in all cases where the patient is reduced to a dangerous condition by loss of blood, to increase the amount of fluid circulating in the vessels. The question then arises as to what solution is best adapted to form a substitute for the lost blood. In cases of exsanguination my experience indicates the superior value of homologous blood over other solutions. The actual risks associated with transfusion of blood in cases of anaemia from ~~ha~~emorrhage are so slight that they need not be regarded, especially when preliminary tests have excluded the dangers of agglutination and haemolysis. With rare exceptions the transfused blood acts as a grafted tissue, and the corpuscles are at once available in the recipient's blood for performing their physiological functions. The serum of the blood also plays an important part in compensating for the volume of fluid lost by haemorrhage.

There has been no evidence of haemolysis or of destruction of the corpuscles in any of my cases of primary or secondary haemorrhage treated by transfusion. The corpuscles appeared to functionate exactly/



exactly like those of the recipient, and presumably their duration in the recipient's blood is that which is normal to the individual patient.

The great advantages of blood transfusion compared with infusion of normal saline or other artificial solutions are:-

- (1) The blood pressure is immediately raised.
- (2) The blood pressure is likely to be maintained.
- (3) The oxygen carrying capacity of the blood is increased.

Naturally one would not recommend transfusion as a routine treatment for loss of blood. It is remarkable how completely and even quickly an individual can recover from loss of blood without special treatment, but there still remain numerous cases where the patient dies from the effects of sudden or prolonged haemorrhage in spite of all treatment, including the usual injections of saline, intravenously or otherwise. My experiments showed that a stage of depletion could be reached, beyond which intravenous injection of saline or Locke's fluid failed to produce any permanent or even temporary response, and which was not compatible with life.

Similar cases may be seen in practice, uncomplicated by shock or toxaemia, where collapse from haemorrhage may be so great that the patient's death is inevitable within a few hours. Apart from extreme/

extreme cases, when death is obviously imminent, it is impossible to lay down any definite rule as to when transfusion is indicated. In traumatic or operation cases the degree of shock present should be taken into consideration, and anti-shock treatment employed in the first instance, if the blood loss has been slight. When, however, the haemorrhage has been considerable, and the patient's condition is critical, transfusion should be preferred.

In recent cases of haemorrhage, haemoglobin estimations and blood counts are not of much assistance, although Depage and Govaerts believe that, if the Red Corpuscles number less than three and a half million per cmm. in the first twelve hours, the case will prove fatal and saline infusions useless. The best indication for transfusion is the presence of signs of serious collapse, such as pallor, sub-normal temperature, a small fast pulse with low blood pressure, restlessness, sighing respirations, syncope or other symptoms of deficient oxygenation. The syncope and collapse which follow a sudden profuse haemorrhage frequently yield rapidly to simple measures, such as raising the foot of the bed and administering fluids; the pulse may be imperceptible only for a few minutes, and quickly recovers its tone and quality. If each case, therefore, is considered on its own merits, transfusion will not be employed unnecessarily. In//

In doubtful cases the blood-pressure is the most valuable index of the gravity of the case.

Continuance of collapse and a rapidly falling blood pressure, when the haemorrhage is controlled, are signs of serious significance, and strongly suggest the necessity for transfusion, particularly when saline infusions and other measures have been tried.

According to Bruce Robertson,<sup>42</sup> the patient's condition is precarious if the blood-pressure is below 70 mm. and when it is below 90 mm. the patient is a bad subject for operation. My own observations confirm these views regarding the significance and dangers of low blood pressure in cases of haemorrhage.

#### I. Transfusion in Cases of Haemorrhage uncomplicated by Shock.

My clinical cases have shown that patients reduced to an extreme degree of collapse from haemorrhage, with air hunger, without pulse, and a blood pressure reduced from 50 to 60 mm. can be immediately revived by a transfusion of blood when other means have completely failed to ameliorate their condition. Case 2, to quote one example, illustrates the remarkable way in which transfusion may reanimate a moribund patient reduced to the condition of the experimental animal which has been bled to the stage at which saline/

saline failed to raise the blood pressure or to maintain life.

Cases 1, 5, and 10 were examples of primary haemorrhage uncomplicated by shock or sepsis. The condition of the patient was critical in these cases and transfusion was the means of saving life.

Cases 7, 8 (second transfusion), and 9 were examples of secondary haemorrhage uncomplicated by shock. In these cases also transfusion was successful in restoring the patient from a moribund condition when other treatment had failed.

Normal saline is not, according to the recent Reports by the members of the Medical Research Committee, the best solution for raising the blood pressure. I have repeatedly observed beneficial results from the intravenous injection of normal saline, but in many cases of shock and of severe haemorrhage the improvement which follows is only temporary and within a short space of time the blood pressure again falls to the original level or even lower than it was before. My own experience with colloidal solutions, which are better adapted for mechanically raising the blood pressure when injected intravenously, is too small to speak from; but in the type of cases mentioned simple elevation of blood pressure may be insufficient to maintain life. Not only//



only the volume of the blood must be increased, but corpuscles also are needed, and these requirements can only be obtained by transfusion of blood, combined if necessary with the infusion of saline or colloidal solution to increase further the amount of fluid within the vessels. Both clinically and experimentally I believe, therefore, that blood transfusion affords a means of saving life in cases of exsanguination when all other methods of treatment have failed.

## II. Transfusion in Cases of Haemorrhage complicated by Shock.

The risks, to which the patient suffering from the effects of haemorrhage is exposed, are aggravated when, as so often happens, an operation under general anaesthesia is necessary, possibly to arrest bleeding or to permit of amputation of a limb or simply to disinfect the parts.

Patients with a low blood pressure, whether from haemorrhage or shock, are notoriously bad subjects for operation, and particularly so if, in addition, there is the element of sepsis present.

Every surgeon has had experience of cases of secondary haemorrhage in which the patient's death has been accelerated by an operation, in spite of subcutaneous or intravenous salines and other methods to/

to combat shock. Local anaesthesia is seldom practicable, and these patients are specially liable to suffer an increase of shock from the anaesthetic as well as from the manipulations during the operation. The question again arises whether the transfusion of blood is not the best means of combating shock in such cases. Certain of my cases bear upon this point.

Cases 2, 3, 4, 6, and 8 (first transfusion) were all examples of patients suffering from shock, combined with haemorrhage, due to an operation. In cases 2, 3, 4 and 6 transfusion was performed after operation, as the patients' condition seemed desperate. In each case the usual anti-shock measures had been employed, and the cases therefore served as an excellent test of the comparative value of blood transfusion. In cases 3, 4, and 6 transfusion proved to be life saving, but it only produced a slight improvement in case 2, and did not prevent death in twenty-four hours.

The facts regarding case 2 require to be considered in the first instance. This patient was suffering from extreme exsanguination following a ruptured ectopic gestation. She had been collapsed for twenty-four hours prior to admission for treatment, and /

and was unconscious when she went on to the operating table. The operation was prolonged and difficult, and there was therefore an increase of shock which further lowered the patient's vitality. Intravenous salines had failed to raise the blood pressure, or to produce any signs of a rally, and transfusion was suggested by the surgeon as a "dernier ressort". Transfusion caused a distinct improvement in the patient's condition. The pulse became palpable, and she regained consciousness a few hours later, but the blood pressure remained low and the pulse small and fast, and death occurred without the patient having recovered from her collapse.

There is no doubt in this case that the patient did not receive a sufficient amount of blood. The transfusion had to be stopped when 500 cc. had been given, as the donor was becoming faint. In such cases of extreme anaemia following haemorrhage 1,000 cc. are probably the ideal amount. While it is impossible to say that a larger transfusion would have saved the patient's life, it is reasonable to conclude that transfusion was not properly tested in this case, although it certainly prolonged life for a few hours.

Case 3 was an example of severe shock combined with a moderate loss of blood. Shock was the predominant feature, and the loss of blood in the absence/

absence of the traumatic shock would have been of slight consequence. The patient, a boy aged nine, was knocked down and dragged by a motor car, the muscles being exposed and bruised over the greater part of one leg from the abdomen downwards. Anti-shock measures improved his condition sufficiently to permit of operation four hours after admission to hospital, but the symptoms of shock became even more pronounced shortly after the commencement of the operation. The value of transfusion was again tested in this case some hours after operation, when the usual methods of treating shock had failed.

While 400 cc. of blood were being transfused the pulse became palpable, and at the conclusion of the transfusion the blood pressure was much higher than it had been before. The improvement following transfusion was maintained, and the subsequent recovery from the condition of profound shock was rapid and complete.

Case 4 illustrates again the value of transfusion in a moribund patient, profoundly anaemic from repeated gastric haemorrhages, and suffering in addition from the effects of starvation for several days, and the immediate shock of an operation for perforation of a gastric ulcer. This patient was suffering from air hunger with respirations of 50 per minute and a blood pressure of 60 mm. mercury.



750 cc. of whole blood had the immediate effect of restoring the patient to consciousness, and in saving her life for the time being. Twelve hours later the blood pressure was 95 and the respirations had fallen to 28 per minute. The patient was apparently well on the road to permanent recovery, when, five days later, a second perforation of the stomach occurred (confirmed post-mortem), which proved fatal within twelve hours. Prior to transfusion the patient had absorbed as much saline as was possible without producing oedema. The effect of the transfusion was to supply the deficiency in corpuscles and to raise the blood pressure and maintain it at a level compatible with life.

The element of shock was also present in case 6, but was less important than the degree of anaemia to which the patient had been reduced by a secondary haemorrhage from the axillary artery.

The patient required ligation of the third part of the sub-clavian artery, and after the operation remained unconscious, collapsed and suffering from air hunger. Anti-shock treatment failed to prevent continued fall of the blood pressure, and at the time of the transfusion it was 65 mm.

The effect of transfusion was remarkable, the patient regained consciousness during the operation.  
Pulse/

Pulse, respiration and blood pressure were all markedly improved, and the patient was able to take a good meal the same evening. Unfortunately a fresh haemorrhage occurred seven days later, when the patient was apparently making excellent progress, and he died within an hour from loss of blood before steps could be taken for transfusing him again.

These cases Nos. 3, 4, and 6 illustrate the positive value of transfusion in cases of haemorrhage combined with post-operative shock. Probably in such cases an equally good, if not better, result could have been obtained if the transfusion had been done shortly before or during the operation. The advantage of transfusion during a major operation, and its effect in preventing further shock in a patient depleted by haemorrhage, is illustrated by case 8.

In this case the patient was reduced to the last degree of exhaustion by repeated secondary haemorrhages from the axillary artery and by septic absorption from gun shot wounds. The patient's condition was desperate as the bleeding point was inaccessible for ligation. In addition the hand was becoming gangrenous and the entire arm was paralysed. The axillary artery could <sup>not</sup> be ligated without an operation under general anaesthesia, but his/

his condition made it extremely doubtful whether he would stand the operation. It was further obvious that simple ligation was insufficient as the arm was useless, and becoming gangrenous and a source of serious danger from the extent and septic nature of the wounds. Disarticulation at the shoulder was indicated, both to facilitate ligation of the axillary artery and to remove the source of septic absorption. As the patient's condition seemed practically hopeless if he were left alone, and as his chances of recovery appeared to be remote if his arm were amputated, unless his condition could be temporarily improved, it was decided to risk the major operation and to perform simultaneously transfusion of blood.

700 cc. of blood were injected while the arm was disarticulated at the shoulder. Improvement in the circulation and blood pressure was noticeable while the operation was in progress. At the beginning of the operation the tissues were almost bloodless, but towards the close numerous bleeding points required to be caught. When the patient returned to bed minus his arm he was in better condition than before the commencement of the operation. In this case transfusion restored the patient from extreme collapse, due to loss of blood, and also diminished the degree of shock from the operation and general anaesthetic/

anaesthetic, the effects of which would otherwise almost certainly have been fatal.

These cases therefore, Nos. 3, 4, 6, and 8 all demonstrate that transfusion of blood is a most valuable procedure in cases of haemorrhage complicated by shock. In all, except case 3, haemorrhage was the main cause of the collapse, although there is no doubt that owing to the loss of blood the degree of shock caused by the operations was considerable. I have had little experience in treating cases of pure shock by transfusion of blood. Case 3 was one in which shock was the primary factor but there had also been a moderate loss of blood. The successful result in this case was due to the fact that the shock, although extreme, had not lasted for more than a few hours, and that the blood pressure was satisfactorily raised and maintained by the transfusion.

Shock was also the outstanding feature of case 10 when a second transfusion was performed. The first transfusion in this case had successfully rallied the patient from collapse following gastric haemorrhage. The second transfusion was performed during a subsequent operation when the patient was in a dying state, and suffering from the effects of starvation/



starvation and prolonged vomiting. It was a question whether the patient would die on the table or not, and the unexpectedly severe nature of the operation required (undoing a posterior gastro-enterostomy and making an anterior gastro-enterostomy) negatived all chance of recovery. It was hoped that transfusion of blood during the operation would give him a chance of recovery, but neither transfusion nor the intravenous injection of 10 ounces of 6 per cent dextrose solution caused any material improvement in the pulse or blood-pressure. Slight improvement in the circulation followed transfusion, but before the operation was completed the patient's condition was even worse than at its commencement.

The case demonstrated that a degree of exhaustion, combined with severe shock, can be reached which will not respond favourably to attempts to raise the blood-pressure or to maintain it by intravenous injections of fluids or of blood.

I have seen cases of recent acute haemorrhage, in which the patient's condition was even more urgent than in this case, revived in the most remarkable manner by transfusion of blood, and I agree with other observers that transfusion is not so successful in relieving patients suffering from extreme shock as in cases of collapse from haemorrhage, or in cases of/

of haemorrhage combined with a moderate degree of shock..

Although in cases of pure shock there is no loss of corpuscles, the volume of the blood is reduced, and there is deficient oxygenation of the tissues, and it is reasonable to believe that the intravenous injection of fluids, which can raise and maintain the blood pressure, would be almost as efficient as blood for this purpose. On the relative merits of blood and gum or gelatine solutions injected intravenously for the treatment of shock, I am not in a position to speak, but I think there is no doubt that the transfusion of blood is more efficacious than infusion of saline in cases of pure shock and further that, when shock is combined with loss of a considerable amount of blood, transfusion of blood is indicated and is the most certain means of saving life.

### III. Transfusion in Cases of Secondary Haemorrhage.

Apart from shock, patients suffering from sepsis are less likely to recover quickly from the loss of blood than when the effects of septic poisoning are absent. Repeated haemorrhages are liable to hasten the patient's death. Sepsis and haemorrhage may produce a vicious circle. Lowered vitality from loss of blood prevents the sepsis from being overcome, /

overcome, and the toxic condition maintains the anaemia. Such patients often require operation, and, therefore, occasions must frequently arise when transfusion of blood is called for.

Cases 6, 7, 8, and 9 were examples of secondary haemorrhage which benefited from transfusion. The facts of case 8 have already been referred to, the patient surviving amputation at the shoulder by the aid of a simultaneous transfusion. The same patient was subsequently revived from a collapsed condition following a fresh haemorrhage from the stump of the axillary artery by a second transfusion, and thereafter progressed to a permanent recovery.

Case 6 had a somewhat similar history, but died from a recurrence of secondary haemorrhage before transfusion could be carried out. As there was no shock in this case there is every reason to believe, that, as on the former occasion, he would have recovered if transfusion had been employed.

Cases 7 and 9 were examples of secondary haemorrhage uncomplicated by shock, and in case 9 the patient was on the point of death when the transfusion was begun.

In reanimating the patients suffering from the effects of secondary haemorrhage, whether combined with shock or not, transfusion proved as successful as in cases of primary haemorrhage.

My/

My cases of secondary haemorrhage are too few to permit of exact deductions being drawn as to the effects of transfusion on the septic infection of the wounds; In case 6 the transfusion had no appreciable effect on the condition of the wounds. In case 8 the patient's general condition improved greatly after the transfusion, but the main cause of this was the removal of large septic areas by amputation. When the haemorrhage recurred about a fortnight after the first transfusion, the element of sepsis was already practically eliminated, and therefore the effect of the second transfusion could be better estimated. \* On this occasion the transfusion apparently not only replaced the blood that was lost, but actively stimulated the formation of fresh corpuscles. Twelve hours after transfusion the red corpuscles were 2,560,000; four days later they numbered 4,050,000 and the improvement in the patient's colour and general condition was remarkable.

Although transfusion was life saving in case 9 it did not improve the local conditions - tuberculous disease of the sacro-iliac joint with mixed infection - and could not be expected to do so.

After transfusion in case 7 the patient made continuous progress. The sepsis quickly diminished, and/



and the temperature became normal within a week.

The impression left in this case was that transfusion had increased the patient's vitality, and thus stimulated his resistance to infection.

It is possible that transfusion may favourably influence the septic process in wounds in three ways:-

1. By diminishing anaemia and improving the patient's general condition and vitality.
2. By stimulating the haemopoietic organs.
3. By the introduction of fresh anti-bacterial or antitoxic substances.

I believe that in certain of my cases the transfusion did raise the patient's resistance to the infection, but there was no evidence that the improvement was specific in nature or due to the protective qualities of the serum of the transfused blood. The practicability of treating a patient by injection of blood from an immune donor, who has either recovered from a similar infection or has been immunised against it, has already been demonstrated by several observers and there is every reason to think that work along these lines will yield useful results in the future.

#### IV. Effects of Transfusion on Arrest of Haemorrhage.

As far as my observations go, transfusion of fresh blood in certain cases improves the spontaneous arrest of haemorrhage. This appears to be the case particularly when the continuance of the haemorrhage is due to conditions, such as haemorrhagic disease of the new born or hemophilia, in which the coagulation time of the blood is prolonged. I have had no opportunity of treating a case of haemophilia, but the results of the cases recorded in literature show that transfusion of healthy blood has a specific action in arresting the bleeding in this disease.

Unger<sup>43</sup> has recorded seven cases of hemophilia in which the bleeding was arrested by a single transfusion of whole blood; in one case, however, two additional transfusions were necessary before the haemorrhage was controlled, and in this case it was found that citrated blood was not so effective as whole blood. In five of the cases the patient's life was saved by the transfusion, after almost every possible means had been tried, without success, to stop the bleeding.

According to Bernheim, as a rule 100 or 200 cc. of blood are sufficient to arrest bleeding, but in cases of exsanguination large amounts can be given with advantage.

Ottenberg, /

Ottenberg, Libman, Petersen and others have had equally good results in hemophilia, finding that the haemophilic's blood will coagulate normally, and bleeding will cease after transfusion of fresh blood. The alarming symptoms are controlled and although the patient is not cured, immunity against recurrence of bleeding is conferred for a variable time. These observers have therefore suggested that small quantities of blood should be injected intravenously at intervals of one to three months. As age advances the tendency to bleed diminishes, and therefore it might be possible to tide over the dangerous period by prophylactic treatment.

Ottenberg and Libman found that fresh serum or defibrinated blood applied to the bleeding point had an undoubted effect on some cases, but that serum introduced subcutaneously or intravenously had no effect on haemorrhage, and did not alter the coagulation time of the haemophilic's blood. Serum treatment had been tried without avail in practically all of their cases of haemophilia in which the bleeding was arrested later by transfusion of blood.

These facts, therefore, demonstrate that transfusion of blood is the method of choice in cases of haemophilia if the symptoms are alarming, or if the bleeding continues in spite of other methods of treatment./

treatment.

The advantage of transfusion is that it not only controls bleeding, but replaces the blood which has been lost, and therefore improves immediately the patient's general condition.

The effect of transfusion in arresting bleeding in the case of haemorrhagic disease of the new-born is as striking as that which follows transfusion in haemophilia. The mortality from melaena neonatorum and other forms of bleeding in the new-born is unfortunately high, and in these conditions there is apparently delay in coagulation.

The value of transfusion was clearly shown in case 1 in which the patient, an infant aged ten hours, was suffering from melaena neonatorum. As the result of intestinal haemorrhage, the child was profoundly anaemic and was reduced to a moribund condition, and, while in this critical state, blood was transfused from the father. Transfusion promptly restored the child to a vigorous condition, and no further bleeding occurred. This operation was done five years ago, and the child is reported to have remained well ever since. The only alternative to transfusion of blood in these cases appears to be the subcutaneous injection of serum or of blood, and there is no doubt that this treatment, introduced by Welch/



Welch in 1910, has greatly reduced the mortality. Robert Hutchison<sup>45</sup> has recently recorded three cases of haemorrhagic disease of the newly-born successfully treated by the subcutaneous injection of whole blood or blood serum in amounts of from 5 to 8 cc. but, although the patients recovered, there was a further haemorrhage in each case.

According to Hutchison it is impossible to say with certainty how serum acts, but it is probable that it supplies some constituent, lacking in the infant's blood, which is necessary for clotting. Hutchison further suggests that normal horse serum or anti-diphtheritic serum would act as well as human serum.

If, as Hutchison suggests, the effect of serum is to raise the coagulability of the blood, it is obvious that the desired effect could be better obtained by intravenous injection of whole blood.

Little notice seems to have been taken in this country of the advantages of transfusion for this condition. As my own case shows, a moribund infant may be almost immediately restored to a healthy condition by transfusion of blood. The value of transfusion in such cases lies not only in the arrest of the haemorrhage, but in the replacement of the blood which has been lost. It is perfectly obvious, therefore, that transfusion can restore patients reduced/

reduced to a stage of collapse, which could not be expected to yield to the subcutaneous injection of small amounts of serum or of blood. This statement is supported by the experience of Unger, who found, that, as in haemophilia, transfusion will save life in cases not helped by subcutaneous injections of serum or of blood.

The intravenous injection of 50 to 100 cc. of whole blood by means of syringes is so simple in infants that there is no object in delaying transfusion in critical cases, which will include the majority, once the diagnosis has been established. In less serious cases transfusion should not be delayed for more than an hour or two, if it is evident that subcutaneous injection of blood or of serum has failed to arrest the bleeding.

I believe that transfusion of blood will sometimes favour the arrest of haemorrhage in cases where the coagulation time of the blood is normal, or at least not materially altered as it is in haemophilia or in infants with a haemorrhagic diathesis. In some cases of repeated bleedings, with the patient becoming progressively more anaemic, there seems to be little tendency for spontaneous clotting to occur even when the coagulation time of the blood is not lengthened. Any clots which form are apt to be soft/

soft and non-adherent and it seems likely that, without altering the coagulability of the blood, transfusion can favour natural arrest by providing a firmer clot.

This result was noted in one of my cases of secondary anaemia (Case 1). The patient was reduced to a profound degree of anaemia by repeated haemorrhages from the haemorrhoidal veins, and he was transfused in order to improve his condition preparatory to operation for an enlarged prostate. The patient's condition was improved by the transfusion as regards his anaemia, and no fresh bleeding occurred in the interval after transfusion till the patient's death, some weeks later, from surgical kidney.

In cases of internal haemorrhage where the bleeding point is not controlled, as in haemorrhage from the stomach or duodenum, it would naturally be concluded that the effect of raising the blood pressure by transfusion would be to increase the haemorrhage, and that the blood which was introduced would quickly be lost again. There is a good deal of clinical evidence to prove that this effect of transfusion need not be greatly feared. It is always a difficult point, in cases of prolonged bleeding from a gastric or duodenal ulcer, to decide whether to keep the patient quiet and to wait for the haemorrhage to cease, /

cease, or to operate. Against operation, there is the fact that in most of these cases the bleeding stops spontaneously, and the patient finally recovers; there is also the possibility that, when the abdomen is opened, the bleeding point cannot be found or satisfactorily secured. If, after hesitating to operate in a case of gastric bleeding, whether from an ulcer or after an operation on the stomach, it is apparent that the bleeding shows no signs of ceasing, and the patient's condition is becoming critical, the risks of operation will be considerable, and such cases will not infrequently die, if operated on, from the combined effects of loss of blood and shock. It is obvious that when the patient is profoundly anaemic his condition could be improved whether an operation has to be performed or not, provided that transfusion does not increase the amount of bleeding. Cases 5 and 10 may be referred to in this connection, as in both of these cases transfusion produced a favourable turn at a period when the patient was becoming progressively more collapsed, and in imminent danger of death from gastric haemorrhage.

Case 5 was transfused as an urgent procedure because of collapse from gastric haemorrhage. At the time of the transfusion the exact cause of the haemorrhage was not determined, the provisional diagnosis being haemorrhage from a gastric vein in relation to/



to cirrhosis of the liver. The patient was pulseless, cold and restless, and gasping for air. 700 cc. of citrated blood were injected with satisfactory result, the patient's symptoms being immediately relieved. The increasing collapse and respiratory embarrassment suggested that the bleeding had continued up to the time of the transfusion, after which no further haemorrhage occurred. Although it cannot be definitely stated that the arrest of the haemorrhage was due to the transfusion, it was at least certain that the improvement in the patient's general condition, and the increase of blood pressure neither prolonged the haemorrhage nor caused it to start afresh.

Case 10 was another example of a case in which it was considered doubtful at the time what the effects of transfusion would be on an uncontrolled bleeding point. Gastro-enterostomy had been performed thirty-six hours previously for duodenal ulcer. Haematemesis commenced soon after the operation, and continued during the period stated. The stitching had been done with great care, and there was some doubt whether the bleeding was from the ulcer, as in a previous case, or from the gastro-enterostomy opening. Three hours before the transfusion the stomach was washed out, and the reddish tinge/.

tinge of the contents showed that there was fresh bleeding at the time. Subsequent to the lavage there was no more sickness, but the patient became steadily more collapsed, and finally was cold, clammy, and pulseless. It was difficult to say if the bleeding had been arrested by the washing out of the stomach, but the fact that he became restless from air hunger and semi-conscious- pointed to its continuance. In any case the effect of the transfusion was immediate, restoring the patient to complete consciousness and improving his pulse and colour, and the improvement in the circulation continued without any recurrence of haemorrhage.

The amount of blood in this case was limited to 500cc. because sufficient improvement followed injection of that amount, and it was considered inadvisable to raise the blood pressure too much in case of exciting fresh haemorrhage.

Although it cannot be definitely stated that in either of the above cases the haemorrhage was arrested by transfusion, the fact is established that transfusion can be done in certain cases of uncontrolled haemorrhage from the stomach with immediate benefit to the patient, and without causing fresh bleeding. In comparison with transfusion the intravenous injection of saline is less efficacious in cases/

cases of exsanguination, and it has the further disadvantage of lessening the coagulating power of the blood, a point of importance where the bleeding is not controlled. Transfusion can be relied upon to improve the patient's condition, at least temporarily, and the evidence shows that when a moderate amount of blood is transfused, coagulation is favoured. Naturally, if the vessel at fault is a large one, transfusion will fail to arrest the bleeding and nothing is likely to save the patient except operation, the risks attendant to which may be very great indeed. Transfusion of blood therefore might conceivably be the only means of rallying the patient sufficiently to enable the operation to be successfully performed. I have observed several patients who have died from continuance of haemorrhage from gastric or duodenal ulcers, or after operations on the stomach, in spite of the usual treatment, whose lives might conceivably have been saved if transfusion had been tried.

The value of transfusion in cases of gastric and duodenal haemorrhage does not appear to have been sufficiently recognised, and, in this connection, I should like to quote the results obtained by Ottenberg and Libman, who record fourteen cases of gastric and duodenal ulcer, all of which were in desperate condition/

condition from severe anaemia and progressive haemorrhage at the time of the transfusion. Twelve of the fourteen cases recovered, the remaining two cases dying from peritonitis or complications of laparotomy. These observers were struck by the fact that in almost all of the cases the haemorrhage stopped after the transfusion.

As regards the relation of transfusion to the recurrence of secondary haemorrhage in septic cases, my impression is that when large arterial trunks are involved, the subsequent immunity of the patient from fresh haemorrhages depends almost entirely on the elimination of the local sepsis. If the septic condition of the wound does not rapidly yield to antiseptic treatment, fresh haemorrhages may occur, possibly hastened by the increased arterial pressure and improvement in the health following transfusion. Other things being equal, the transfusion undoubtedly will speed up the reparative process, which unfortunately is slower in the coats of the infected artery than in the surrounding tissues. Frequently in these cases the artery may be found buried in healthy granulation tissue, and yet, when it is ligated for a secondary haemorrhage, the vessel wall is still soft and friable. The infection seems to cling to the/



the stumps both of ligated arteries and of nerve trunks after the surrounding parts have become clean and healthy.

In chronic cases of sepsis, associated with repeated small haemorrhages, transfusion may stimulate the patient's power of resistance, and indirectly prevent subsequent bleedings, but, as far as I have seen, the local treatment is the important factor in the prevention and arrest of haemorrhage due to sepsis.

CONCLUSIONS REGARDING THE VALUE OF TRANSFUSION OF  
BLOOD IN CASES OF PRIMARY AND SECONDARY HAEMORRHAGE.

1. Transfusion is frequently life saving, when other treatment for the constitutional effects of haemorrhage has failed.
2. It diminishes the amount of shock during operations on exsanguinated cases.
3. It has a restorative effect in cases suffering from the combined effects of haemorrhage and shock, either traumatic or operative, when other treatment has failed.
4. It can raise and maintain the blood pressure and restore patients suffering from severe shock when other treatment for shock has failed.
5. Transfusion has a specific action in haemorrhagic disease of the newly-born, arresting the haemorrhage and permanently restoring the patient to health.
6. Transfusion has a specific action in haemophilia, and is the most certain means of arresting bleeding in this disease. Immunity against recurrence of haemorrhage is conferred for a variable time.

7. The immediate response to transfusion is as pronounced in cases of secondary haemorrhage as in primary haemorrhage.
8. Transfusion may improve the patient's resistance to infection and indirectly hasten healing of septic wounds.
9. Transfusion will, in certain cases of anaemia, associated with repeated small bleedings, favour the natural arrest of haemorrhage.
10. Transfusion may save life in cases of uncontrolled gastric or duodenal haemorrhage, and in such cases encourages the arrest of bleeding, by improving the quality of the clot. When the bleeding has ceased spontaneously the transfusion of a moderate amount of blood is unlikely to excite fresh haemorrhage.
11. The local treatment of septic wounds is the most important factor in preventing a recurrence of secondary haemorrhage, and transfusion can only indirectly diminish the risk of bleeding.
12. When local sepsis persists in the tissues around a large artery ligated for secondary haemorrhage, transfusion has little influence in preventing a recurrence of the bleeding, and may possibly hasten it by increasing the blood pressure.

Although there may be considerable difference of opinion regarding the indications for transfusion- I think one is justified in saying that the medical profession as a whole is not yet sufficiently alive to the value of blood transfusion in critical cases of primary or secondary haemorrhage. It was only in the last year or two of the recent war that military surgeons began to use transfusion freely in treating these cases and the papers published by Archibald,<sup>46</sup> Primrose and Ryerson,<sup>47</sup> O. Robertson,<sup>48</sup> Bruce Robertson,<sup>49</sup> Lee,<sup>35</sup> Hull<sup>50</sup> and others, have demonstrated once and for all the wonderful results which may follow transfusion in suitable cases of haemorrhage or of haemorrhage and shock. There is no doubt however that the scope and indications for transfusion are not yet thoroughly realised by civil practitioners, and there must be many surgical, medical and obstetrical cases which die from haemorrhage without transfusion having been attempted, suggested, or even thought of. I am not aware of a single instance in recent years in which transfusion has been employed in Edinburgh in a case of Placenta Praevia or of Postpartum haemorrhage: certainly no such cases have been recorded or come to my notice.

Looking/



Looking back on my own limited experience I can recall several patients who died from haemorrhage after prostatectomy, thyroidectomy, gastro-enterostomy, splenectomy, nephrectomy, or from injury, in spite of injection of saline and other measures, and whose lives, I feel now, might possibly have been saved if blood had been transfused.

OBSERVATIONS ON CASES OF SECONDARY ANAEMIA  
TREATED BY TRANSFUSION.

This series includes six cases in which eight transfusions of blood were performed. It is convenient to divide the cases into two groups.

(a) Cases of Secondary Anaemia following haemorrhage or the postpartum state.

There were three cases in this group.

Case 1. The patient was suffering from symptoms of enlarged prostate and severe anaemia due to repeated bleedings from internal piles.

Transfusion was performed in order to raise the patient's vitality sufficiently to justify the risks of operation.

Cases 2 and 3. Both patients became anaemic after child birth at which there was excessive bleeding.

Transfusion was performed in case 2 because the patient was moribund, and in case 3 because the anaemia was progressive in spite of the usual medical treatment.

(b) Cases of malnutrition associated with Secondary Anaemia.

Cases 4, 5 and 6. The patients were infants aged six months, seven weeks and three months respectively./

respectively. Cases 4 and 5 were marasmic and atrophic infants suffering from gastro-intestinal disturbance and intolerance of food. The symptoms in case 6 were due to acute gastro-enteritis.

Transfusion was employed in each case as the condition of the patients was critical and cases 5 and 6 were moribund.

DISCUSSION REGARDING THE VALUE OF TRANSFUSION  
IN CASES OF SECONDARY ANAEMIA.

Secondary anaemia may result from so many different conditions that it is impossible to classify the cases in one group, although the type of anaemia, characterised by a diminution of red corpuscles and a low colour index, is common to all forms. The anaemia may be due to active haemolysis of the corpuscles, or to repeated haemorrhages or continued loss of small amounts of blood; in other cases it is associated with the toxæmia of bacterial infection or of malignant disease; or it may be due simply to mal-nutrition.

The conditions which lead to secondary anaemia could be further detailed, but it is sufficient to point out the important bearing which the etiology has upon the prognosis of the individual case and its amenability to treatment.

As the alteration in the blood is necessarily a gradual process the patient can suffer from a much greater degree of anaemia, and the symptoms may be less pronounced, than in cases of recent profuse haemorrhage./



haemorrhage. Transfusion of blood, therefore, when called for, will not be employed as an emergency measure, and in most cases it will be considered only when the usual measures of treatment, appropriate to the case, have failed.

The cases which are most likely to be benefitted by transfusion are those in which the anaemia is secondary to haemorrhage, and in which toxic and septic factors are absent. But even in these cases, and especially where the anaemia has been profound or of long duration, the chances of recovery are likely to be affected by degenerative and other secondary changes in the organs. The simple addition of fresh blood, while likely to be beneficial, cannot produce such a remarkable transformation in the patient's appearance and symptoms, as in cases of acute haemorrhage when the tissues and organs are presumably normal. Complete recovery, in the cases requiring transfusion, is bound to be gradual, whatever method of treatment is adopted.

A./

A. Cases of Secondary Anaemia following haemorrhage or the Postpartum state.

In my three cases with a history of haemorrhage there was evidence that, although the haemorrhage may have been an important cause of the anaemia, a second factor was present which was partly responsible for the condition of the blood.

In case 1 there was infection of the genito-urinary tract which ultimately caused the patient's death and was, in all probability, partly responsible for the anaemia. Infection of the uterus, following upon postpartum haemorrhage, was the primary cause of the blood destruction in case 2; the failure of this case to respond to treatment must be attributed chiefly to the secondary changes in the organs resulting from profound anaemia and toxæmia. In case 3 the anaemia, although only pronounced after postpartum haemorrhage, was already evident during pregnancy, and it must be presumed that some toxic factor peculiar to that state was mainly responsible for the anaemia.

Some benefit was derived from transfusion in each case, although two of the patients subsequently died. No serious reaction followed transfusion and there was no reason to regret having tried it.

The/

The reasons for transfusion were different in each of the three cases, and illustrate what are likely to be common indications for transfusion in secondary anaemia.

Case 1. The object of the transfusion in this case was to raise the patient's vitality in order that a major operation might be attempted with reasonable prospects of success. The anaemia was due to repeated loss of blood extending over a number of years, and latterly profuse in amount. The bleeding was from internal piles, which were specially troublesome because of the straining due to difficulty in micturition from enlargement of the prostate. Removal of the piles and prostatectomy were indicated, but the patient's condition was so weak that the question of prostatectomy could not be considered. The red corpuscles were reduced to 1,800,000 and the haemoglobin to less than 20%. According to Miculicz patients with a haemoglobin percentage of less than 30% are not fit subjects for operation, and this rule applies with special force to cases where there is likely to be shock and loss of blood.

It was hoped that by transfusion the patient would be sufficiently improved to justify the risk of operation, and the immediate effect was satisfactory./

satisfactory. The red corpuscles were increased to 3,100,000 and the haemoglobin to 45%. The blood pressure was raised from 120 to 130 mm. of mercury and at the same time the pulse rate was diminished from 110 to 100 per minute. The patient not only looked but felt better, and it was hoped that the transfusion would stimulate the patient's natural power of recovery. It was accordingly decided to postpone operation until he was still further improved. In the meantime symptoms of surgical kidney developed and the patient died from pyelo-nephritis without operation having been attempted.

It was interesting to note in this case that the improvement in the condition of the blood was maintained till the patient's death and also that no further haemorrhages occurred. It can be claimed therefore that the transfusion was justified, and that, had the kidneys not become infected, the object of the transfusion would in all probability have been attained.

I think it is safe to say that, when precautions are taken in selecting the donor, transfusion offers a means of improving the chances of patients who are bad subjects for operation, on account of secondary anaemia. If transfusion is performed immediately prior to operation it may sufficiently improve the condition/



condition of the patient to permit of an operation being attempted, which, otherwise would be almost certainly fatal. Even in cases of secondary anaemia due to mal-nutrition, or associated with the cachexia of malignant disease, one is justified in believing that the patient's powers of resistance could be enhanced by a preliminary transfusion, and such cases have in fact been recorded.

Transfusion for Progressive Anaemia secondary to  
Pregnancy and the postpartum state.

Case 2. The patient in this case\* was suffering from anaemia of a secondary type, similar to that of certain of the cases recently described by Osler.<sup>51</sup> The anaemia was out of all proportion to the amount of blood lost at parturition, and was probably more dependent on infection of the uterus, as indicated by the history, than loss of blood. Some active toxin must have been present, although the source was not apparent when the patient was observed in hospital, as, in a period of less than three weeks immediately prior to transfusion during which the patient was under medical treatment, the red corpuscles had diminished from 2,500,000 to 600,000, and the haemoglobin from 40% to less than 10%, without any fresh haemorrhage to account for the/

the alteration in the blood.

Death was imminent when transfusion was suggested. The immediate effect of the transfusion was encouraging, the patient regaining consciousness; the pulse also was improved as regards its rate and volume, and the blood pressure increased from 20 to 100 mm. of mercury. The red corpuscles per cubic mm. were more than doubled and the haemoglobin was raised from 10% to 30%. The improvement in the colour and general condition of the patient was maintained for ten days; but there was no evidence of the bone marrow having been stimulated. The improvement coincided only with the duration of the grafted corpuscles, and after ten days the anaemia again became progressive, the patient's death occurring three weeks after the transfusion. Although the final result was disappointing there was no doubt that transfusion prolonged the patient's life, and this in itself was sufficient to justify the operation.

The impression left by this case was that transfusion should be tried in critical cases of secondary anaemia when the cause of the anaemia does not preclude the possibility of a permanent recovery. Naturally the chances of permanent success will be greater if transfusion is not postponed till the patient/

patient is in extremis, and its employment should at least be considered when the anaemia is progressive in spite of treatment, or even if the patient's condition remains stationary. A repetition of the transfusion might be worth trying in similar cases, particularly when the general condition of the patient is not hopeless.

The conclusions derived from the above case were confirmed by the favourable effects of transfusion in case 3, in which the anaemia was of a somewhat similar type, but less advanced.

Case 3. The symptoms of anaemia in this case began during pregnancy, but became more pronounced after parturition, at which there was excessive haemorrhage. There was nothing to suggest sepsis or any factor, other than the pregnancy and the postpartum haemorrhage, to account for the symptoms. The reduction of the corpuscles and of the haemoglobin were not specially marked, but the symptoms of weakness and oedema about the legs indicated considerable constitutional disturbance. While in the medical wards of the R.I.E. the patient received the usual treatment for secondary anaemia, but her symptoms did not improve and the anaemia was progressive. In sixteen days, during which she was getting iron, the red corpuscles fell from 4,500,000/

4,500,000 to 3,400,000 and the haemoglobin from 65% to 45%. Transfusion was therefore recommended by the physician, and this was carried out with immediate benefit. The haemoglobin was raised to 80% and the improvement was maintained, the red corpuscles increasing finally to 4,680,000, when the patient left hospital much improved.

The transfusion not only replaced the deficiency in red corpuscles, but also stimulated the bone marrow and arrested definitely the progress of the anaemia. The operation was therefore justified by the subsequent result, and the case illustrates the value of blood as a therapeutic agent.

Many of my cases of chronic anaemia from different causes, have only had the chance of benefit from transfusion when the patient was extremely feeble and the prospects of recovery were remote. As large amounts of blood are not necessary there is no reason why transfusion should not be more often recommended in cases of secondary anaemia, which fail to respond to ordinary methods of treatment. Fresh compatible blood may not only improve the patient's condition, but may also stimulate the haemo-poietic organs to the formation of better corpuscles, or to a greater output of corpuscles than were produced prior to the transfusion.



(b) Cases of Mal-nutrition associated with Secondary Anaemia.

Although marasmus is not a disease the term is useful to describe the atrophic condition of infants suffering from mal-nutrition due to inability to assimilate food. The difficulty in feeding may be present from birth, particularly in premature infants or those born with low vitality. Some of the congenital cases are specific, and the wasting may be the only symptom of the disease. When the condition is acquired, it is frequently due to improper feeding and these cases are more amenable to treatment. Gastro-enteritis is often present and it may be difficult to say whether the irritability of the alimentary tract is a cause or effect of the condition.

Continued vomiting and diarrhoea make the giving of an adequate amount of fluids impossible, and it may be necessary to supplement a restricted diet by subcutaneous injections of saline, dextrose and olive oil. Although life can be maintained for short periods by this means, the child's weight is likely to remain stationary, or to diminish, and the condition is certain to be fatal, unless normal feeding can soon be resumed.

Cases 4 and 5 were feeble infants at birth and both were suffering from vomiting and .  
diarrhoea and inability to digest milk  
or/

or to assimilate sufficient fluids of any kind. Both were suffering from marasmus and were extreme examples of this atrophic state.

Case 6 was suffering from acute gastro-enteritis and previously had been a healthy child.

Subcutaneous injections of dextrose and of olive oil were necessary in each case to keep the child alive.

The patients were pallid, wasted and wrinkled, presenting the prematurely aged appearance characteristic of the condition. The features were pinched and the trunk and limbs shrunken. All the patients were suffering from anaemia secondary to the malnutrition and gastro-enteritis. In case 6 the red corpuscles were 4, 200,000; Haemoglobin 65% and white corpuscles 31,200. This shows a considerable reduction of red corpuscles and of haemoglobin, when compared with a normal count of an infant of the same age (three months), which should be, according to John Thomson, red corpuscles 5,000,000, haemoglobin 85%, white corpuscles, 12,000.

The ages and weight of the cases were as follows:-

	Age.	Weight.
Case 4	6 months	9 lbs 4 ozs.
5	7 weeks	4 lb. 2 ozs.
6	8 weeks	6 lb. 4 ozs.

The object of transfusion, in case 4, was to increase the vitality of the infant, in the hope that its powers of digestion and assimilation of food might be increased. Prior to transfusion the weight had remained stationary for a period of 6 weeks. The child was able to take very little nourishment and what it did take seemed to do it no good. While not in immediate danger, it was felt that no progress was being made and that, unless there was some change for the better, the child could not continue to live much longer.

Transfusion causes a striking alteration for the better in the colour and appearance of the marasmic patient. The injection of 40 ccs. of blood into the longitudinal sinus had a stimulating effect in case 4; For several days the child was lively and took its food much better. The serum of the blood introduced must have been partly responsible for the benefit, but I believe that the correction of the anaemia was still more important, and the improvement in digestion was apparently associated with the richer blood supply and the better functional activity of the organs concerned.

Reference to the chart of this case ( Fig. 19. ) shows that the weight increased after the transfusion, and/



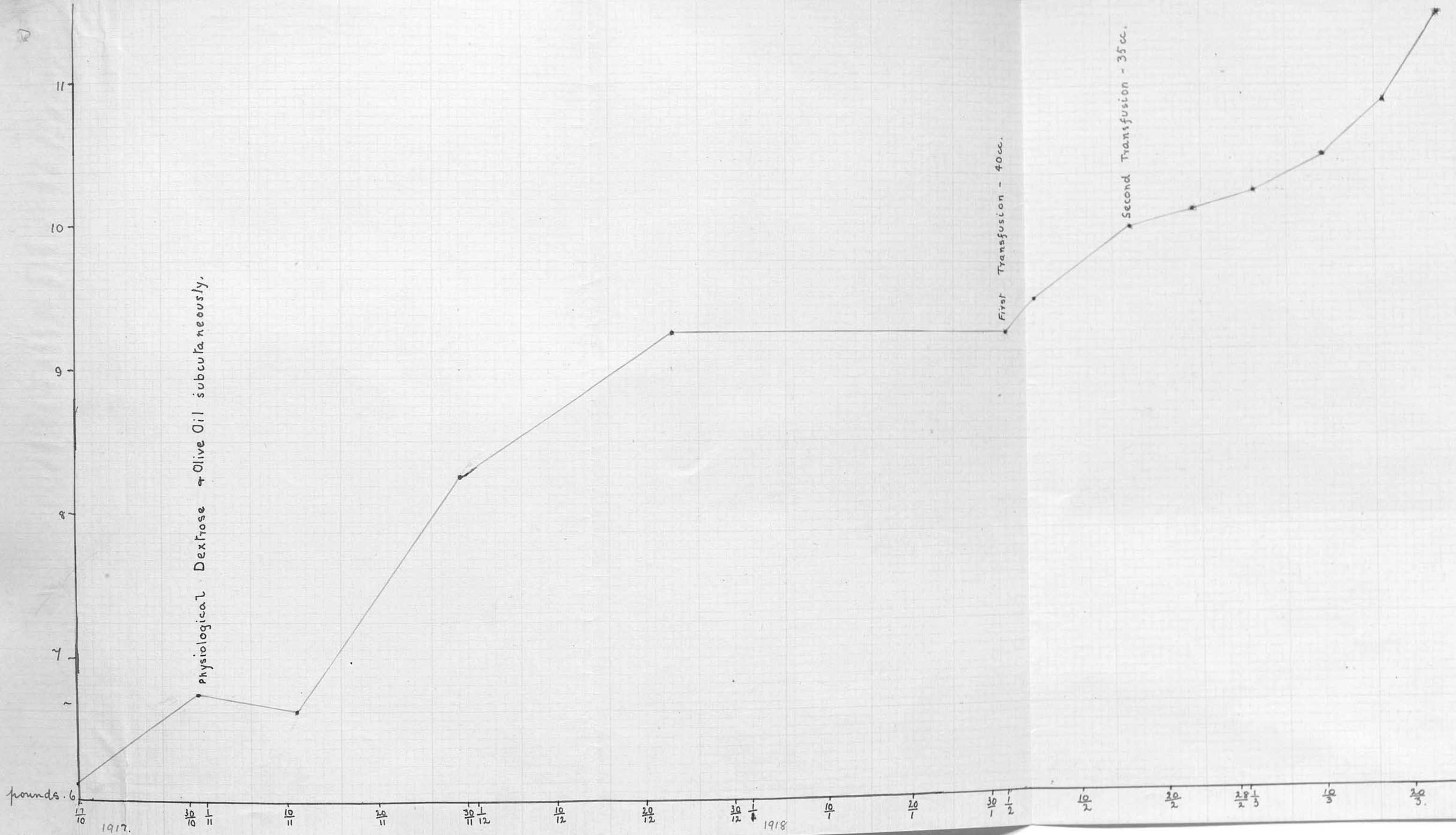


Fig. 19. Chart showing the effect of repeated Transfusion on the weight of a Marasmic Infant. Case IV.



and particularly after a second transfusion of 35 cc. of blood, which was given fifteen days later. Transfusion did not immediately abolish the tendency to vomiting, but it certainly initiated recovery, and three weeks after the second transfusion all digestive troubles had ceased and the signs of marasmus had disappeared.

In cases 5 and 6 transfusion was resorted to as a final attempt to postpone what appeared to be imminent death. It can safely be said that no harm resulted from the transfusions and, particularly in case 5, where the transfusion was repeated, that the infant's life was prolonged and it was given a chance of recovery. In both cases transfusion produced an immediate improvement in the child's appearance and condition, but in case 6 this was only transitory, as the acute gastro-enteritis, which was entirely responsible for the wasting, persisted. The benefit which followed transfusion was more definite in case 5. For a few days he was able to take a fair amount of nourishment and the weight increased from 4 lbs. to 4 lbs. 6 ozs. in eight days, but, thereafter, vomiting returned and the condition of the patient again became critical. In spite of a temporary improvement following a second transfusion, the intolerance to food persisted and the child died a fortnight later.

It/

It will thus be seen that the effects of transfusion were much more encouraging in the cases of marasmus than in the case of acute gastro-enteritis;

There was little ground for believing, in the last case, that transfusion would do much good. Everything else had been tried and the favourable results, observed in the cases of marasmus previously treated, were the chief reason for trying transfusion. When rapid wasting, anaemia and collapse are due to an infective condition, associated in its early stages with fever, and death is imminent, the injection of blood is unlikely to prevent death, or to prolong life materially, if the infective process still remains active. There is no reason, however, why transfusion should not be tried as a last resort. The chances of recovery and of a fatal issue are often so finely balanced that, in a small proportion of critical cases, transfusion of blood might turn the scale in the direction of recovery.

My experience of Transfusion in cases of marasmus, associated with mal-nutrition and Secondary Anaemia, is too limited to permit of definite conclusions being drawn; but the results obtained, in the two cases recorded, were sufficiently favourable to indicate that this method of treatment should be employed more often in the future. I believe that the/

the reasons for transfusion in atrophic infants are sound. When, under the usual treatment, the gastrointestinal disturbance subsides and normal feeding can be resumed, the signs of anaemia soon disappear. It is therefore reasonable to believe that the converse may sometimes follow, and that, if the anaemia is corrected, the patients powers of assimilating nourishment, and the general condition, will also improve. Transfusion of blood should be considered when the symptoms of marasmus persist, in spite of medical and dietetic treatment, or when subcutaneous or intravenous alimentation are necessary to maintain life. The transfused blood cannot be expected to act as an efficient substitute for food. More nourishment can be administered by subcutaneous or intravenous injection of dextrose and other fluids. Transfusion, therefore, is not to be considered as an alternative to other methods of treatment, but as an additional means which, by improving the quality of the blood, may possibly act as a stimulus to the organs of digestion, the physiological functions of which are in abeyance.

CONCLUSIONS.

1. Transfusion of blood is a valuable means of treatment in certain cases of secondary anaemia.
2. The cases which are most likely to be benefited are those in which the anaemia is secondary to haemorrhage, and in which toxic and septic factors are absent, or of minor importance.
3. The immediate effect of transfusion is to improve the patient's general condition (a) by raising the blood count and haemoglobin percentage; (b) by increasing the volume and diminishing the rate of the pulse; (c) by raising the blood pressure.
4. Transfusion of blood is indicated in cases of secondary anaemia requiring operation when the haemoglobin percentage is at a dangerously low level (less than 30% or possibly 40%)
5. Transfusion of blood may initiate a spontaneous recovery after the usual treatment has failed to arrest the progress of the anaemia.
6. Its employment should be considered when the usual treatment appropriate to the case has failed to arrest the progress of the anaemia or when the patient's condition remains stationary.



7. Complete recovery, when it occurs, will be more gradual than in cases of primary haemorrhage treated by transfusion.
8. Patients who are moribund and unconscious as a result of profound anaemia and toxæmia may regain consciousness and life may be prolonged for a short period. A repetition of the transfusion should be considered in such cases when there is an absence of reaction on the part of the bone marrow and the symptoms relapse.
9. Transfusion should not be postponed till the patient is in extremis, as the secondary changes in the tissues and organs, associated with prolonged anaemia or toxæmia, may render permanent recovery impossible.
10. Cases of Marasmus due to mal-nutrition and gastro-enteritis suffer from a moderate degree of secondary anaemia.
11. Transfusion of whole blood into the longitudinal sinus or a subcutaneous vein is a simple and harmless procedure in infants, when compatible blood is selected.
12. Transfusion causes a striking improvement in the/

the appearance and vitality of the marasmic patient and the haemoglobin can be raised to the normal level.

13. Transfusion may prolong life or initiate recovery in critical cases of marasmus, by increasing the vitality of the infant and by improving the digestion and assimilation of food; it should be repeated if the improvement is only temporary.
14. Transfusion is indicated in marasmic infants when the condition is critical or the child is moribund; but it is to be considered as an accessory, and not as an alternative, to other means of treatment.
15. Transfusion is unlikely to be beneficial in cases of wasting and collapse due to acute gastro-enteritis.

OBSERVATIONS ON CASES OF PURPURA TREATED  
BY TRANSFUSION. (2 cases).

The milder forms of Purpura usually recover spontaneously or under medical treatment, while the severer cases are frequently fatal and resist all attempts at treatment. It is only in the severer forms of purpura, characterised by secondary anaemia and by haemorrhages into the tissues and mucous membranes, that transfusion needs to be considered as a possible means of treatment. Ottenburg and Libman<sup>44</sup>, Petersen<sup>53</sup>, and Unger<sup>43</sup> have recorded a sufficient number of cases (twenty-three) to show that, in a considerable proportion, there is a prompt cessation of the haemorrhages and an improvement in the general condition, coincident with the correction of the anaemia. In the severer types, however, there is little evidence afforded to suggest that the progress of the disease is often curtailed. The effect of transfusion in arresting the tendency to haemorrhages is commented upon by all observers. It is well known that in Purpura Haemorrhagica the blood-platelets are reduced in number, especially before and during the occurrence of haemorrhage. Ottenburg and Libman suggest that, as the coagulation time of the blood is little altered, the haemostatic effect of transfused blood is due to the introduction of fresh/

fresh platelets. As the normal duration of blood-platelets in the circulation is known to be short, it is obvious that the continued freedom from recurrence of haemorrhage, which is occasionally observed, is not sufficiently explained by this theory.

When it is remembered that the etiology of Purpura is still obscure a satisfactory explanation of the effects of transfusion cannot be expected.

My own experience is limited to two cases.

In Case 1 the transfusion was recommended by the physician as an emergency operation. The patient was collapsed, as a result of a profuse haemorrhage from the bowel, and was obviously dying. Death occurred within twenty-four hours and transfusion, therefore, was not successful in prolonging life.

Temporary improvement followed transfusion in Case 2; but the patient died five weeks later. In this case, as in the former, the patient was profoundly anaemic; and there had been bleeding both into the skin and from the mucous membranes. During the exposure of the patient's vein there was excessive oozing of blood from the tissues of the wound. The interesting observation was made that the capillary bleeding was arrested by the transfusion. Although the patient's condition was temporarily improved/



improved, transfusion did not have any curative effect. While in my own cases the results of transfusion were disappointing, the recorded cases show that occasionally transfusion enabled the patient to tide over a critical period. Further observations, therefore, are required before any expression of opinion would be justified regarding the value of the procedure.

OBSERVATIONS ON TRANSFUSION OF BLOOD  
IN PERNICIOUS ANAEMIA.

There is still considerable difference of opinion regarding the value of transfusion in Pernicious Anaemia. Some of the earliest observations on the subject were made in this school and the paper read by Brakenridge<sup>52</sup> before the Edinburgh Medico-Chirurgical Society in 1892 aroused considerable interest. The results obtained by Brakenridge in a series of five cases were most encouraging, but the subsequent experience of other physicians was scarcely so satisfactory, and Hunter, to quote one authority, not only denied the value of transfusion but regarded it as positively harmful.

Although different methods of transfusion have been employed, in most of the earlier cases sodium phosphate was mixed with the blood to inhibit coagulation. The value of anti-coagulants for purposes of transfusion has been amply demonstrated by the successful results obtained, formerly with sodium phosphate and recently with sodium citrate, in cases of haemorrhage. The use of substances which alter materially the character of the blood can scarcely be considered the ideal method of transfusion in conditions such as pernicious anaemia. The observations/

observations which I made in one case, which was transfused twice from the same donor, illustrate the relative value of modified blood and whole blood. On the first occasion citrated blood was used without benefit; fourteen days later the same amount of blood was transfused directly from vein to vein and the subsequent improvement in the patient's symptoms and the blood counts proved that the corpuscles were well maintained in the circulation.

The improvements in technique which have been evolved during the last decade and the introduction of methods of testing the compatibility of the bloods before transfusion justify a fresh investigation of the effects of transfusion in a disease such as pernicious anaemia.

The progress of cases of pernicious anaemia is so capricious that, unless a considerable series of cases can be recorded, the conclusions derived from any one form of treatment cannot be relied on. There have been comparatively few observations made on the effects of transfusion in pernicious anaemia by writers in this country since the modern technique of whole blood transfusion has been established. It is my object therefore to analyse the results obtained in a series of twenty-one cases of pernicious anaemia and to draw from the facts observed conclusions regarding the value of transfusion in this disease;

Analysis/

Analysis of Pernicious Anaemia Cases  
treated by Transfusion.

<u>Number of cases.</u>		21
<u>Sex.</u>		
	Male	7
	Female	14
<u>Age.</u>	Between 20 30	1
	30 40	7
	40 50	2
	50 60	5
	60 70	6

Duration of Symptoms in 20 cases. (1 unstated)

Less than 1 year	8 cases
Between 1 and 2 years	8 cases
Between 3 and 6 years	4 cases

In sixteen of the cases transfusion was called for within two years or less of the first symptoms of anaemia. In eleven of the cases the patient had suffered from one or two relapses. In nine cases, according to the history, the symptoms were progressive.

Number of transfusions 24

Three cases were transfused twice, Nos. 9, 12 and 20.

Number of red blood corpuscles per cubic millimetre  
at time of transfusion (estimated before 21  
transfusions.)

Less than 1,000,000 per c.m.m.	13
Between 1,000,000 and 1,300,000	8



Haemoglobin percentage at time of Transfusion.

Less than 20%	5
Between 20 and 30%	12
Between 30 and 32%	4

Methods adopted for Transfusion.

Whole blood	23
Direct transfusion (artery to vein)	19
Vein to vein	4
Citrated Blood	1

Reasons for Transfusion.

The cases will be described in two groups according to the reasons for transfusion:-

Group A. In nine cases, Nos. 1, 2, 3, 4, 9A, 10, 15, 19 and 21, transfusion was recommended because the patients appeared to be dying. All these patients were in a state of profound collapse and, with the exception of cases 2, 10 and 19, were semi-conscious or comatose at the commencement of the transfusion.

Group B. In the remaining cases, all of whom were seriously ill, transfusion was recommended because the anaemia was progressive or stationary in spite of the usual medical treatment.

Reasons/

Reasons for Transfusion a second time.

A second transfusion was performed on three cases.

Case 9. A second transfusion was performed because the patient was becoming moribund. Slight improvement had followed the first transfusion and the second transfusion was done at the request of the patient's relatives.

Case 12. The patient's condition improved after the first transfusion but after a period of intermission the symptoms relapsed. A fresh remission followed the second transfusion.

Case 20. Transfusion was repeated in this case because the symptoms had not been improved. A fresh remission followed the second transfusion.

In these cases the first and second transfusion are referred to as 9A, 9B, 12A<sup>12B</sup> and 20A, 20B respectively.

GROUP A.

Cases of Pernicious Anaemia treated by Transfusion because the patients were moribund or apparently dying.

Case 21./

Case 21. was in articulo mortis at the commencement of the operation and died two minutes before the actual transference of blood began.

The transfusion of blood from the radial artery of the patient's son was continued for a few minutes, but the attempt to resuscitate the case failed.

Red Blood Corpuscle Count and Haemoglobin percentage immediately before and after transfusion.

	<u>R.B.C.</u>	<u>Haemoglobin.</u>
Case 1.	Before 900,000	Before 30
	After 1,300,000	After 50
	Increase 400,000	Increase 20%
Case 2.	Before 500,000	Before 15
	After 950,000	After 25
	Increase 450,000	Increase 10%
Case 3.	Before 710,000	Before 21
	After 1,850,000	After 45
	Increase 1,140,000	Increase 24%
Case 4.	Before 480,000	Before 13
	After 1,250,000	After 30
	Increase 770,000	Increase 20%
Case 9B.	Before 590,000	Before 12 15
	After 885,000	After 17
	Increase 295,000	Increase 3%

	<u>R.B.C.</u>	<u>Haemoglobin.</u>
Case 10.	Before 1,000,000	Before 30
	---	After 40
	---	Increase 10%
Case 15.	Before 500,000	Before 14
	After 630,000	After 16
	Increase 130,000	Increase 2%
Case 19	Before 920,000	Before 30
	After 1,320,000	After 45
	Increase 400,000	Increase 15%

Except in cases 9B and 15 the increase in red corpuscles and in the haemoglobin was sufficient, if deficient oxygenation had been the sole factor, to resuscitate the patients. The associated secondary changes, due to the profound anaemia, are sufficient to explain why the simple elevation of the blood count is less effective in cases of collapse from pernicious anaemia than in cases of primary haemorrhage, where the tissues and organs are more likely to be normal.

#### Immediate effect of transfusion.

In each case the additional blood produced an improvement in the colour of the patient's skin and mucous membranes.

No improvement in the patient's condition was observed in Cases 9B and 15.



Immediate benefit was observed in cases 1, 2, 3, 4, 10 and 19. Cases 1, 3 and 4, previously unconscious, regained consciousness during the transfusion.

Transfusion revived case 4 in a remarkable fashion. For several days prior to transfusion she had been troubled with sickness and unable to take nourishment. Latterly there was incontinence and unconsciousness increasing to coma. As the patient's colour began to improve she became conscious and although at first dazed and bewildered she became quite rational before the transfusion was completed and took an intelligent interest in what was going on.

#### Progress after Transfusion.

No improvement. Death within twenty-four hours. Cases 9B and 15. The patients did not regain consciousness and life was little if at all prolonged.

Temporary improvement. Cases 1, 10 and 19. Case 1. The patient's general condition was distinctly improved for a few days. No remission set in and death occurred 15 days after transmission.

Blood/

Blood Counts before and after Transmission.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
26.11.13	1,300,000	--	30%	1.15
3.12.13	1,275,000	--	40%	1.60
7.12.13 (B.T.)	900,000	9,000	30%	1.67
(A.T.)	1,300,000	--	50%	1.83
8.12.13	1,300,000	--	-	-
9.12.13	1,300,000	--	-	-
10.12.13	1,200,000	--	-	-
13.12.13	980,000	--	35%	1.79
15.12.13	1,100,000	--	40%	1.83
20.12.13	1,000,000	--	35%	1.75

It is obvious in this case that the transfused corpuscles were more or less maintained for a few days in the circulation. There was no evidence however of reaction on the part of the bone marrow and, therefore, the improvement following transfusion was brief, and death ensued, as was to be expected from the patient's condition.

Case 10. The patient was sufficiently revived by the transfusion to insist on her removal home on the same day. The anaemia had developed rapidly in this case and was associated with jaundice. The transfused corpuscles were rapidly destroyed, the patient dying four days later.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
22.2.15.	3,400,000	6,600	64%	.9
5.4.15 (B.T.)	1,000,000	23,000	30%	1.5
(A.T.)	--	--	40%	-
9.4.15	450,000	24,000	-	-

There was no reaction in this case suggestive of a gross incompatibility of the blood. Haemolysis had been particularly active for a period of six weeks before transfusion, as indicated by the fall in the blood count and by the presence of jaundice.

Case 19. The patient was better for a few days after transfusion; cardiac murmurs disappeared and there was no severe reaction. The patient died one week after transfusion and at the post-mortem numerous petechial haemorrhages were found in the skin, pleurae and mucous membrane of the colon. The caecum and colon were distended and the contents offensive. There was fatty infiltration and degeneration of the left ventricle. The bone marrow was pale and showed an absence of reaction.

Continued//

Continued improvement followed by a remission.

Cases 2, 3 and 4.

Case 2. The patient tolerated arsenic better after the transfusion and the red corpuscles and haemoglobin were gradually increased.

The patient was in good health six months later when last seen.

Case 3. The immediate benefit was continued. The patient was in good health four years later.

Blood Counts before and after Transfusion. Case 3.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
1.12.14	770,000	8,000	19%	1.20
8.12.14(B.T.)	710,000	7,300	21%	1.30
(A.T.)	1,850,000	6,200	45%	1.20
9.12.14	2,520,000	--	45%	.90
11.12.14	2,800,000	--	48%	.80
13.12.14	2,640,000	8,800	45%	.80
18.12.14	2,590,000	5,000	40%	.77
23.12.14	2,400,000	6,300	42%	.80
30.12.14	3,750,000	8,500	55%	.70
4.1.15	3,700,000	7,600	56%	.70
5.1.15	3,900,000	---	60%	.70
8.1.15	3,900,000	---	65%	.80
20.1.15	4,210,000	5,400	65%	.70



This patient was receiving arsenic both before and after transfusion. The blood chart shows that her condition was stationary. The symptoms were more marked than the degree of anaemia. She was semi-conscious at the commencement of the transfusion during which she regained consciousness and spoke intelligently. The successive blood counts show that the transfused blood corpuscles were maintained and that a fresh remission was started.

Case 4. The immediate improvement was maintained, life was prolonged and a slight remission was initiated. Death occurred seven weeks after transfusion.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
17.9.14	1,620,000	3,100	36%	1.
1.1.15(B.T.)	480,000	1,100	13%	1.3
3.1.15(A.T.)	1,250,000	500	30%	1.2
28.1.15	1,230,000	1,000	23%	1.3
12.2.15	1,075,000	3,300	30%	1.4
18.2.15	670,000	1,000	15%	1.1

The transfused corpuscles were retained in the circulation and the blood count kept approximately to the level reached after transfusion by reaction of/

of the marrow, which however was not maintained for more than a short period. The final fall in the blood count was subsequent to a cold which the patient developed six days before death.

In the above nine cases transfusion was attempted only as a "dernier ressort". The patients had been treated with arsenic and other medical measures without arresting the progressive nature of the anaemia, and the symptoms in each case were such that the patient's death, within a few hours or a few days at most, seemed inevitable. It is well known of course that, even in apparently hopeless cases of pernicious anaemia, the symptoms may occasionally suddenly abate and a fresh remission may commence. I think, however, that there can be no doubt that in the three cases here recorded - Nos. 2, 3 and 4 - transfusion proved to be life-saving, and that the subsequent remission resulted directly from the transfusion of blood. The effects of transfusion were particularly striking in cases 2 and 3, and in the latter case the patient has survived more than four years, in spite of a subsequent relapse, and when recently communicated with she was reported to be enjoying good health.

Although the proportion of recoveries in the above series of cases is small, the fact is established/

established that transfusion of blood can resuscitate patients suffering from pernicious anaemia when all other means have been tried in vain. In cases of profound anaemia, which have failed to react to ordinary medical measures, it seems only reasonable that, if transfusion is to be tried at all, it should not be postponed till the patient is in extremis. Several of the cases in this series were moribund or so far reduced that the operation could hold out but little prospect of bringing about their recovery. The facts of the following case will illustrate this point.

Case 21. On the recommendation of a physician, a female patient, aged 35, was sent across to the surgical side for transfusion of blood. The patient had been under treatment for several weeks for pernicious anaemia, and, in spite of the usual measures, her condition had gone from bad to worse. When brought into the operating theatre, the patient was obviously dying. She was unconscious, pulseless, cold and clammy. Her eyes were sunken and glazed; her respirations were fast and feeble; and there was an ominous rattle in her throat. Her son had come by arrangement to act as donor; and, against my better judgement - convinced that the patient was "in articulo mortis" - it was decided/

decided to go on with the operation. Unfortunately, the patient died two minutes before the actual transfusion was started and the last steps of the operation were a race against time. The donor's blood was allowed to enter the patient's veins for a few minutes, in an attempt at resuscitation, but the stethoscope showed that the heart did not resume beating.

A similar case may be mentioned in which the patient died while being transferred from the medical side to the operating theatre for transfusion. These cases of course are extreme, but they illustrate a tendency that exists, in cases where the operation of transfusion has been considered, to delay the procedure till too late. Such cases are likely to bring discredit on the method.



GROUP B.

Cases of Pernicious Anaemia treated by Transfusion  
because the Anaemia was progressive or stationary in  
spite of the usual medical treatment.

Transfusion was employed on fifteen occasions in the thirteen cases of this series because the anaemia was progressive or the symptoms persisted in spite of medical treatment. The patients were seriously ill but not in immediate danger of dying.

Red Blood Corpuscle Count per cubic millimetre and  
Haemoglobin percentage immediately before and after  
Transfusion.

	R.B.C..	Hb.
Case 5.	B. 600,000	B. 18
	A. 1,240,000	A. 36
	Increase 640,000	Increase 18
Case 6.	B. 1,030,000	B. 25
	A. 1,770,000	A. 40
	Increase 740,000	Increase 15.
Case 7.	B. 1,280,000	B. 25
	A. 2,400,000	A. 48
	Increase 1,120,000	Increase 23
Case 8.	B. 1,110,000	B. 24
	A. 2,560,000	A. 46
	Increase 1,450,000	Increase 22

	R.B.C.	Hb.
Case 9A.	B. 1,200,000	B. 32
	A. 1,800,000	A. 44
	Increase 600,000	Increase 12
Case 11.	B. 1,140,000	B. 28
	A. 2,050,000	A. 40
	Increase 910,000	Increase 12.
Case 12A.	B. 280,000	B. 24
	A. 2,660,000	A. 52
	Increase 1,680,000	Increase 28
Case 12B.	B. 200,000	B. 28
	A. 2,500,000	A. 73
	Increase 1,600,000	Increase 45.
Case 13.	B. 1,100,000	B. 22
	A. 3,500,000	A. 55
	Increase 2,400,000	Increase 33.
Case 14.	B. ---	B. 30
	A. ---	A. 45
		Increase 15.
Case 16.	B. 1,000,000	B. 25
	A. ---	A. -
Case 18	B. 800,000	B. 20
	A. ---	A. 30
		Increase 10

	R.B.C.	Hb.
Case 20A.	B. 637,000	B. 15
	A. 1,925,000	A. 25
	Increase 1,288,000	Increase 10
Case 20B.	B. 777,000	B. 20
	A. 1,775,000	A. 30
	Increase 998,000	Increase 10

#### Immediate Effects of Transfusion.

The haemoglobin was increased by at least 10% after transfusion and frequently by more. An immediate improvement in the patient's colour was noticed in each case and, as a general rule, the alteration in the patient's appearance was striking. Cases 6, 7 and 8 became much brighter mentally, and in case 18 the patient noticed that her sight was at once improved.

Cases 9A, 11, 12A, 12B, 13, 16, 17, 20A and 20B. expressed themselves as feeling better and stronger.

#### Effects of Transfusion on Blood Pressure.

The systolic blood pressure was estimated in four cases.

	Before Transfusion;	After Transfusion.	Increase;
Case 5.	106	130	24 mm of Hg;
" 6	118	126	8 " "
" 7	100	130	30 " "
" 20	104	118	14 " "

Effects of Transfusion on Pulse Rate.

The immediate effect of transfusion was to improve the volume of the pulse in every case, at least temporarily. The pulse rate was occasionally faster for twenty-four or forth-eight hours. In cases in which the transfusion had a beneficial effect, and in which a remission was started, the pulse improved in quality and gradually became slower after transfusion. This was observed in cases 5, 7, 12A, 12B, 13, 16; 18 and 20B. When the improvement was continued, but only to a slight extent, the pulse rate did not diminish in frequency.

Evidence of Reaction or harmful effect during or after Transfusion.

None of the patients suffered from serious symptoms suggestive of gross incompatibility of the blood. The following immediate or subsequent signs of reaction were noticed.

1. Oppression. Case 50 suffered from temporary cyanosis, oppression and difficulty in breathing due to an over transfusion. The symptoms passed off within a few minutes.



2. Vomiting. Case 14 became flushed and vomited during the transfusion. This was due to incompatibility of the blood.

Subsequent haemolysis occurred, as shown by an icteric tinge in the skin, which developed on the third day after transfusion, but no haemoglobinuria was present. The patient's temperature was elevated for several days, but no subsequent harm resulted.

3. Rigors. None occurred in any of the cases.

4. Pain in the Back. No patient complained of this.

5. Oedema. Case 12B developed oedema around the left eye which was closed for a few minutes. This occurred during a second transfusion, from the same donor, and was probably a serum reaction. The patient felt no discomfort and there was no other signs of reaction, except an elevation of temperature to  $99.8^{\circ}$  on the same evening, and the subsequent progress was satisfactory.

6. Temperature reaction. There was a subsequent elevation of temperature in nine cases as follows.-

Case	53	100.6
	6	100
	7	102
	12A	99.8
	12B	99.8
	13	100.2
	14	"Marked rise"
	20A	101
	20B	104

7. Jaundice. This sign of haemolysis was noted in case 14.
8. Haemoglobinuria. This was not observed in any of the cases.

The results of the transfusions in this series show that the dangers and risks of transfusion even in cases where the blood has not previously been tested, are not great. Case 14 was the only one in which incompatibility was obvious and the patient did not suffer seriously from the haemolysis of the transfused corpuscles. The greatest temperature reactions occurred in the case (No. 20), transfused twice from the same donor, in which the precaution had been taken beforehand, of testing the donor's and recipient's bloods for agglutination and haemolysis. The temperature reactions so frequently observed did not affect the subsequent progress of the cases.

#### Progress subsequent to Transfusion.

##### Temporary improvement not followed by a remission.

In the following five cases the transfusion, while not producing any harmful effect, and sometimes followed by a temporary improvement, failed to cause a fresh remission. The patients died within a short period after the transfusion.. It will be noted in regard/

regard to case 20, however, that benefit followed a second transfusion. In the following table the duration of life after transfusion is noted.

Case 8	Death 9 weeks after transfusion.			
" 2A.	" 6 "	" "	" "	" "
" 14	" 36 days	" "	" "	" "
" 17.	" 4 months	" "	" "	" "
" 20A.	" 9 $\frac{1}{2}$ "	" "	" "	" "

The principal facts regarding these cases are as follows:-

Case 8. This was an acute case with symptoms of six weeks duration prior to transfusion. Arsenic had failed to improve the condition of the blood.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
2.3.15	1,060,000	4,400	24%	1.20
8.3.15 Arsenic	---	--	-	-
18.3.15 (B.T.)	1,110,000	4,800	24%	1.09
(A.T.)	2,560,000	4,000	46%	.90
22.3.15	2,100,000	--	46%	1.00
27.3.15	2,090,000	--	42%	1.05
10.4.15	1,290,000	1,100	28%	1.17
25.4.15	1,180,000	1,000	26%	1.20
7.5.15	900,000	--	22%	1.20
12.5.15 P. dismissed.				

From the records of the blood counts it is seen that the transfused corpuscles were fairly well preserved for nine days after transfusion. There was no reaction, however, on the part of the bone marrow, and the blood picture reverted within a few weeks to its original condition.

Case 2A. This patient had been steadily going downhill after several years of treatment.

Arsenic had entirely lost its effect.

Temporary benefit followed transfusion; the patient looked and felt stronger and had a better appetite, but, as the accompanying table shows, there was no fresh remission. A second transfusion was performed when the patient was in a dying condition, without prolonging her life.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
8.3.15 (B.T.)	1,200,000	3,000	32	1.3
12.3.15 (A.T.)	1,800,000	3,400	44	1.2
29.3.15	1,800,000	3,000	36	1.0
21.4.15 (B.T.)	590,000	--	12.15	1.2
22.4.15 (A.T.)	885,000	--	17	.9

Case 14. Transfusion was tried as the patient was becoming weaker, after several years of illness, and was not responding to arsenic.

The haemoglobin was raised 15% at the transfusion, but within three days, although no examination of /



of the blood was made, all the corpuscles must have been destroyed, as the patient became jaundiced and lost the fresh colour he had gained. The patient regained his appetite and improved to a slight extent after the reaction, due to haemolysis, was over; but the bone marrow appeared to be exhausted and death occurred in six weeks time.

Blood Counts before and after Transfusion.

Date.	R.B.C.	H.b.
5.4.16	1,450,000	35
8.4.16 (B.T.)	--	(B.T.) 30
(A.T.)	--	(A.T.) 45
30.4.16	1,400,000	33

Case 17. In this case the patient was suffering from a relapse within nine months of the onset of the first symptoms of pernicious anaemia. The anaemia was comparatively slight and the blood had considerably improved as the result of treatment. In spite of the haemoglobin having been raised from 56 to 75% the symptoms of weakness, breathlessness, etc., were not relieved, and transfusion was suggested by the physician on that account. The following table of blood counts shows that transfusion, while raising the haemoglobin from 75 to 85%, had no permanent effect and the anaemia soon became more marked than it was before.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
17.10.16	1,850,000	11,000	56%	1.50
29.10.16	3,770,000	4,500	75%	1.00
1.11.16 (A.T.)	--	--	85%	-
12.11.16	3,330,000	--	85%	1.20
28.11.16	3,880,000	--	85%	.90
9.1.17	2,700,000	6,000	55%	1.00

Case 20A. The symptoms of this case began about nine months before transfusion and the patient was already suffering from a relapse.

Arsenic was well tolerated but ineffective. The accompanying table shows that the blood count had reverted practically to its former level three days after transfusion of 450 cc. of citrated blood. It is possible that the citrate solution had diminished the resistance of the corpuscles as a repetition of the transfusion from the same donor was successful.

Blood Counts.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
26.1.18 (B.T.)	637,000	3,870	15%	1.4
(A.T.)	1,925,000	4,600	25%	-
27.1.18	1,687,000	4,460	28%	-
28.1.18	1,287,500	4,300	20%	-
29.1.18	880,000	3,940	18%	-
30.1.18	925,000	3,950	18-20%	-
31.1.18	950,000	4,050	20%	-

The observations made on these five cases show, therefore that, in a considerable proportion of cases of pernicious anaemia which are refractory to the usual treatment (33.3%), transfusion of blood also will fail to improve the blood picture, except for a brief period, or to prolong life.

Continued Improvement followed by Remission.

In the following ten cases the immediate benefit conferred by transfusion was continued; a fresh remission of the symptoms was initiated and the patients' lives were possibly prolonged. In all of the cases the symptoms relapsed and none survived longer than from four to sixteen months after transfusion. The duration of life after transfusion is indicated in the following table.

Case 5.	Death in 13 months.	---
" 6.	" " 10 "	---
" 7.	" " 12 "	---
" 11.	" " 10 "	---
" 12A.) 12B.)	" " 16 "	Transfused twice. Remission after each Transfusion.
" 13	" " 6 "	---
" 16	" " 4 "	---
" 18	-----	History after leaving hospital unknown.
" 20B.	" " 8 months	---

The cases will be divided into two groups and considered separately according to whether arsenic had been given before transfusion or not.

A. Observations on the Effects of Transfusion of Blood in cases of Pernicious Anaemia not treated with Arsenic immediately before or after Transfusion.

In four cases, numbers 5, 6, 7 and 11, all of which benefited by transfusion, no arsenic was given immediately prior to the transfusion, or for a short period thereafter, so that the effects of transfusion on the progress of the cases could be studied without any complicating factor.

Case 5. The following table of blood counts shows that the transfused corpuscles remained intact in the circulation. The subsequent blood counts, prior to the administration of arsenic, remained at much the same level as that reached immediately after the transfusion. It is obvious that the patient was maintaining the improved condition by the output of her own corpuscles, but that the improvement was not progressive till arsenic was administered. Arsenic therefore was the important factor in the continued though short remission which followed transfusion.

Blood/



Blood Counts before and after Transfusion.      Case 5.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
23.1.15	630,000	3,400	20%	1.60
2.2.15 (B.T.)	600,000	6,000	18%	1.50
(A.T.)	1,240,000	6,200	36%	1.50
6.2.15	1,050,000	5,300	30%	1.50
10.2.15	1,200,000	6,500	25%	1.04
18.2.15	1,260,000	8,000	30%	1.20
27.2.15	1,280,000	--	38%	1.40
5.3.15 (Arsenic)	---	--	-	-
12.3.15	2,300,000	5,300	42%	.90
13.3.15 (P. left Hospital)		--	-	-
27.3.15	2,770,000	--	50%	.90
18.3.16	1,140,000	3,400	26%	1.20

Case 6. The improvement following transfusion was maintained, but the remission produced was only slight. The administration of arsenic had no immediate effect although subsequently the remission became more marked. The facts of the case suggest that arsenic was the important factor in the remission which followed transfusion.

Blood./

Blood Counts before and after Transfusion.

Date.	R.B.C..	W.B.C..	Hb.	C.I.
26.1.15.	1,660,000	7,400	30%	1.30
2.2.15. (B.T.)	1,030,000	6,300	25%	1.10
(A.T.)	1,770,000	7,000	40%	1.10
4.2.15.	1,600,000	--	38%	1.10
8.2.15.	1,940,000	--	44%	1.10
16.2.15.	1,560,000	5,200	34%	1.10
26.2.15.	1,850,000	5,200	36%	1.20
5.3.15 (Arsenic)	---	--	-	-
11.3.15.	1,540,000	4,000	36%	1.20
17.3.15.	1,480,000	--	34%	1.20
26.3.15.	1,770,000	4,600	35%	1.02
P. left hospital				
27.3.15	---	--	-	-
11.5.15.	2,400,000	--	60%	1.30

Case 7. Arsenic also appeared to be more effective in this case than the transfusion. When arsenic was given, one week after the transfusion, it was apparent that, although the patient was still greatly improved, the improvement was not progressive.

Blood/

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
10.2.15	1,500,000	4,300	35%	1.10
16.2.15 (B.T.)	1,280,000	3,500	25%	1.04
(A.T.)	2,400,000	3,600	48%	1.00
23.2.15	2,070,000	4,000	40%	1.00
24.2.15 (Arsenic)	--	--	-	-
2.3.15	2,560,000	4,400	50%	1.00
11.3.15	2,710,000	6,200	57%	1.05
31.3.15	3,600,000	--	66%	.90
3.4.15	3,780,000	6,200	65%	1.10

Case 11. In this case also the administration of arsenic was the more important factor in the comparatively slight remission which followed transfusion, although nine days after transfusion, as the blood counts show, the corpuscles and haemoglobin were still considerably increased compared to their proportions prior to the operation.

Blood Counts before and after Transfusion.

Date.	R.B.C.	Hb.	C.I.
1.4.15 (B.T.)	1,140,000	28%	1.3
8.4.15 (A.T.)	2,050,000	40%	1.
9.4.15	1,400,000	30%	1.07
10.4.15	1,550,000	34%	1.1
12.4.15 (Arsenic)	--	-	-
15.4.15/			

Date.	R.B.C.	Hb.	C.I.
15.4.15.	2,200,000	40%	0.9
22.4.15	2,160,000	33%	0.8
10.5.15.	2,550,000	40%	0.8
20.5.15.	2,610,000	42%	0.75
16.9.15.	1,430,000	30%	1.07

The above four cases show, therefore, that while transfusion alone may diminish the anaemia a fresh remission does not necessarily follow unless arsenic is given. It is obvious in these cases that arsenic, given from the first, might equally well have produced the results ultimately obtained. On the other hand it is also reasonable to believe that the undoubted improvement in the condition of the blood and in the patient's general health, which was due to the transfusion, prepared the way for, and favoured the subsequent response to arsenic.

The remaining cases of this series received arsenic both before and after transfusion and the remission which followed can be fairly attributed to the transfusion of blood.

Observations/



B. Observations on cases of Pernicious Anaemia in which Arsenic had failed to produce a remission and which benefited by Transfusion.

Case 12A. and B. Two Transfusions.

Blood Counts before and after Transfusions.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
20.3.15 (B.T.)	980,000	1,000	24%	1.3
26.3.15 (A.T.)	2,660,000	3,200	52%	.98
27.3.15	2,300,000	3,200	48%	.96
28.3.15	2,470,000	3,600	46%	.94
29.3.15	2,720,000	4,800	49%	.89
31.3.15	2,600,000	5,600	46%	.89
3.4.15	2,180,000	4,800	46%	1.04
11.4.15	2,300,000	4,000	45%	.98
18.4.15	1,950,000	5,000	47%	1.2
4.5.15	1,970,000	4,000	45%	1.1
22.5.15	2,400,000	--	54%	1.1
2.10.15 (B.T.)	900,000	6,000	28%	1.5
(A.T.)	2,500,000	3,600	73%	1.4
4.12.15	3,000,000	--	90%	1.5

Judged by the increase in the blood count alone, the patient's condition was much improved by transfusion on both occasions. The patient had been in hospital for eighteen days and had received arsenic for ten days, without improvement, before transfusion was/

was advised. The transfusion started a fresh remission of the symptoms. The increase of corpuscles and of haemoglobin was well maintained except for a temporary decline of the blood count, as indicated in the tables, associated with excessive doses of arsenic and gastro-intestinal disturbance. Remission after the first transfusion was not prolonged but transfusion again had a remarkable effect as is shown in the table of blood counts.

Case 13. This case had been in hospital and had received arsenic for a month before transfusion was performed. The anaemia had not yielded to treatment and his condition was stationary prior to transfusion.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
17.1.16	1,400,000	6,000	20%	.81
7.2.16	1,000,000	2,500	20%	1.00
12.2.16 (B.T.)	1,100,000	3,000	22%	1.00
(A.T.)	---	---	65%	-
13.2.16	3,500,000	5,000	55%	.79
16.2.16	2,400,000	---	40%	.83
29.2.16	2,500,000	6,000	35%	.70
13.3.16	3,170,000	6,400	40%	.64
20.3.16	2,600,000	5,000	40%	.77
26.3.16	2,060,000	4,500	40%	1.00
14.4.16	2,390,000	8,000	30%	.65

Date.	R.B.C.	W.B.C.	Hb.	C.I.
18.4.16	3,000,000	-	60%	1.00
9.5.16	2,250,000	-	44%	1.00
16.5.16	2,720,000	-	58%	1.04
22.5.16	2,000,000	-	60%	1.50

The remarkable increase in the red blood corpuscles and haemoglobin which immediately followed transfusion was associated with improvement in the patient's symptoms. The subsequent counts did not vary much, but they were made over a period of fourteen weeks, which was sufficiently long to show that the continued improvement was due to a fresh remission and reaction on the part of the marrow.

Case 16. This patient had been ill for a few months only and had become progressively weaker and more anaemic in spite of the usual treatment including arsenic. Only two observations on the blood, as indicated below, were made, but the improvement, both immediate and subsequent to transfusion, was undoubted. The patient recovered sufficiently to return to work for a short period.

Blood Counts before and after Transfusion.

Date.	R.B.C.	Hb.	C.I.
25.5.16 (B.T.)	1,000,000	25	1.25
(A.T.)	---	-	-
28.6.16	1,520,000	35	1.1

Case 18. This patient had been ill for two years and at the time of the transfusion was very weak. Arsenic had entirely failed to arrest the progress of the anaemia. Observations on the blood were made immediately before and after transfusion but not subsequently. The haemoglobin was raised from 20 to 30%. After transfusion the patient made steady progress and a fresh remission was initiated.

Case 20. This case was transfused twice and the facts of the first transfusion have already been referred to. The second transfusion was performed thirteen days later and was successful. The patient had previously benefited from arsenic but had suffered a relapse, and on this occasion neither arsenic nor the first transfusion of citrated blood improved the blood count. From the accompanying table it is apparent that the corpuscles were maintained after the second transfusion with whole blood, and that the continuance of the improvement was due to the fresh output of corpuscles. The second transfusion supplied the stimulus to the bone marrow necessary for the onset of a remission.

Blood/



Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.
26.1.18 (B.T.)	637,000	3,870	15%
(A.T.)	1,925,000	4,600	25%
27.1.18	1,687,000	4,460	28%
28.1.18	1,287,500	4,300	20%
29.1.18	880,000	3,940	18%
30.1.18	925,000	3,950	18 - 20%
31.1.18	950,000	4,050	20%
9.2.18 (B.T.)	777,500	2,083	20%
(A.T.)	1,775,000	4,486	30%
10.2.18	1,875,000	4,760	29%
11.2.18	1,687,500	4,160	28%
12.2.18	1,650,000	4,761	26%
13.2.18	1,575,000	4,583	26%
21.2.18	1,900,000	3,750	28%
28.2.18	1,950,000	4,000	28%
5.3.18	1,937,000	--	34%

It will thus be seen that transfusion was beneficial and instrumental in starting a fresh remission in ten out of 15 cases of Pernicious Anaemia which were seriously but not critically ill. In four of the ten cases which benefited, however, arsenic was the more important factor in the subsequent remission. In the remaining six cases transfusion succeeded in initiating/

initiating a fresh remission of the symptoms when arsenic had been tried prior to transfusion without effect.

From the description of the cases in groups A. and B. it is obvious that the effects of transfusion in refractory cases of pernicious anaemia cannot be readily anticipated. Patients in a semi-conscious and dying state may occasionally be revived in the most remarkable manner, while other cases, not so seriously ill, may receive no benefit. The main features of the cases which did not benefit by transfusion are shown in the following table.

Characteristic Features of Cases of Pernicious Anaemia not benefitted by transfusion.

A. Moribund or apparently dying cases.

Case.	Duration of Symptoms	R.B.C.	Hb.	C.I.	Death after Transfusion.
1.	7 months	900,000	30	1.67	15 days
9B.	5 years	570,000	12-15	1.2	24 hrs.
10.	18 months	1,000,000	30	1.5	4 days
15.	6 months	500,000	15	1.5	24 "
19	2 years	920,000	30	1.7	7 "

B. Cases seriously ill but not moribund.

8	8 weeks	1,110,000	24	1.09	9 weeks
9A.	5 years	1,200,000	32	1.3	6 "
14	4 "	1,450,000	35	1.2	36 days
17	9 months	---	-	-	4 months
20A.	9 "	637,000	15	1.4	9 "

In the above cases transfusion did little to arrest the progress of the anaemia or to prolong life. All of the cases had been treated previous to transfusion in the usual way without success and, except in case 17, the anaemia was progressive in spite of treatment.

Two of the cases, cases 9B and 14, were of a chronic type and transfusion was tried without effect in the terminal stages of the disease. Cases 8 and 15 were of an acute type, and anaemia having been progressive since the onset of symptoms. In the remaining cases also the symptoms were of comparatively short duration and relapses had already occurred. Five of the cases were regarded as being critically ill and in all of them the symptoms were pronounced and, except in case 17, there was pyrexia. In one case, No. 10, the blood destruction had been particularly rapid for a few weeks prior to transfusion and the patient was jaundiced; except in this case and in two others there was a history of haemorrhages having occurred.

The colour index of these cases, although varying considerably, was on the whole higher than in the cases which were benefited by transfusion. Except in cases 15, 19 and 20A. the blood corpuscles and haemoglobin were not reduced to a specially low degree, and the severity of the symptoms was often greater than the examination of the blood would have suggest-

suggested; this could be attributed either to the acuteness of the anaemia or to the pronounced secondary changes in the organs. The blood films showed the absence of reaction on the part of the bone marrow, but the type of cells varied to a considerable extent; the observations were not sufficiently detailed to establish a typical picture for this group of cases, or to enable the prognosis to be deduced accurately from the appearance of the films.

The failure of case 20A to improve was attributed to the use of the citrate method of transfusion.

Characteristic Features of Cases of Pernicious Anaemia  
benefitted by Transfusion.

A. Moribund or apparently dying cases.

Case.	Duration of Symptoms.	R.B.C.	Hb.	C.I.	Death after Transfusion.
2.	3½ years	700,000	25	1.7	Alive 6 mths. later.
3.	9 months	710,000	21	1.3	Alive 4 yrs. later.
4.	10 "	480,000	13	1.3	7 weeks

B.//



B. Cases seriously ill but not moribund.

5.	1 year 9 mths.	600,000	18	1.55	13 months
6.	1 year	1,030,000	25	1.1	10 "
7.	1 "	1,280,000	25	1.04	12 "
11.	1 "	1,140,000	28	1.3	10 "
12A.	6 "	950,000	24	1.3	16 "
12B.	--	900,000	28	1.5	---
13.	15 mths.	1,100,000	22	1.0	6 months
16.	Several months	1,000,000	25	1.25	4 "
18	2 years	800,000	20	1.2	---
20B.	10 mths.	770,000	20	1.3	10 months.

In the above cases, which responded to transfusion and in which there was a remission of the symptoms for a variable period, there was no outstanding feature which enabled the effects of transfusion to be anticipated or which characterised the group. The degree of anaemia was quite as marked as in the cases which transfusion failed to benefit, and some of the cases were semi-conscious or dying at the time of transfusion. The colour index was not as a rule so high and the duration of the symptoms was rather longer than in the previous group. In most of the cases in this group the temperature was either normal or only slightly irregular, and the/

the absence of a marked evening rise of temperature undoubtedly increases the prospects of benefit from transfusion. For this reason I think it is probable that the irregular temperature in pernicious anaemia is partly due to toxæmia and not solely to the presence of anaemia.

Effects of Transfusion on the Symptoms and Signs of  
Pernicious Anaemia.

It was observed in the cases with an irregular temperature which responded to transfusion that the temperature gradually returned to the normal and remained normal as long as the progress was continued. The beneficial effect of transfusion showed itself in various ways and was most striking in the cases which were critically ill at the time of the transfusion. Most of the patients were dull and apathetic and their mental processes were immediately stimulated by the increased volume of blood in circulation. In favourable cases the symptoms attributable to deficiency of the circulation, such as shortness of breath and palpitation, became less noticeable and often were markedly relieved.

Effect/

### Effect of Transfusion on Gastro-intestinal Symptoms.

It was frequently noted that the appetite and powers of digestion were increased, and this of course in itself was an important factor in the patient's recovery. Many of the patients suffered from nausea, vomiting, and diarrhoea, and frequently it was impossible either to feed them or to treat them adequately with arsenic.

The severer gastro-intestinal symptoms, commonly present in advanced cases, do not necessarily disappear immediately as the result of treatment directed solely to the correction of the anaemia. The septic condition of the intestinal tract may be responsible for the dyspeptic symptoms. Certain of my cases, however, recovered their appetite and lost the nausea and sickness so soon after transfusion that it seemed probable that the profound degree of the anaemia was responsible for the symptoms. Deficient oxygenation must interfere with the functions of the digestive organs, and the patient's capacity for assimilating nourishment may therefore be immediately improved by the reduction of the anaemia by transfusion.

### Effects of Transfusion on the Administration of Arsenic.

The administration of arsenic after transfusion contributed largely to the subsequent progress of the cases; and there is no doubt from the history of/  
of/

of the cases that arsenic is often not only more effective but also better tolerated after the transfusion than it was before. This was brought out especially in cases 2, 4 and 16.

In case 2 the patient was suffering from a second relapse of the anaemia. Arsenic was given before but had to be stopped because of continuous vomiting, retching and diarrhoea. The patient was in a state of collapse, but was revived by transfusion following which the nausea and vomiting ceased and feeding could be resumed. Arsenic was given on the fourth day after transfusion and continued thereafter with most beneficial results. The subsequent progress of the case was uninterrupted and is shown in the accompanying table.

Blood Counts before and after Transfusion.

Date.	R.B.C.	W.B.C.	Hb.	C.I.
28.2.14	770,000	-	20%	1.3
8.3.14 (B.T.)	500,000	-	15%	1.5
(A.T.)	950,000	-	25%	1.2
12.3.14(Arsenic)	1,000,000	-	26%	1.3
15.3.14	1,200,000	-	30%	1.25
25.3.14	1,400,000	-	35%	1.25
28.4.14	2,250,000	-	50%	1.10
13.5.14	2,500,000	-	65%	1.30

There//



There is no question as to the relative value of arsenic and transfusion of blood as a means of treatment. Arsenic is apparently the most successful and reliable therapeutic agent at present available in pernicious anaemia. Transfusion cannot be regarded as a substitute for arsenic but it is undoubtedly an adjuvant, which, as my cases show, will sometimes stimulate the bone marrow afresh, and lead to a remission when arsenic cannot be tolerated or has been given without effect.

#### Effects of Transfusion on the Blood Counts and Films.

Signs of improvement are indicated by the increase in red blood corpuscles and haemoglobin as shown by successive counts and by alteration in the character of the films. Following transfusion the white corpuscles are increased in number and in cases which benefit the leucopaenia subsequently becomes less pronounced.

The colour index is immediately lowered by transfusion and, while in some cases it returns to its former high level, in others it gradually decreases as the symptoms improve. In case 12 after the first transfusion the colour index was reduced from 1.3 to .98, and remained approximately normal while the patient was improving under treatment.

When/

When this patient left hospital the colour index was 1.1. The same patient was readmitted after a subsequent relapse and on this occasion the colour index was 1.5 but was reduced to 1.4 by transfusion. Two months later, on her leaving hospital again, much improved with the red corpuscles increased from 900,000 to 3,000,000, the colour index was still high and the symptoms not long afterwards relapsed, the patient dying six months later.

### Case 3.

This case also illustrates the modification of the characteristically high colour index following successful treatment and the onset of a remission which was undoubtedly initiated by transfusion. The colour index was 1.3 immediately before transfusion. The blood count taken on the same day after the transfusion was much improved and the colour index was 1.2. On ten subsequent occasions, during a period of six weeks, the colour index remained below 1.0, but five months later, when the patient was readmitted suffering from a relapse, the colour index was again high (1.5).

In cases improving under treatment the colour index as a rule became less than it was before, but the diminution was rarely so marked as in the cases quoted above.

The/

The blood films made immediately after transfusion generally present a very different appearance to those made immediately before the introduction of fresh blood. Two types of erythrocytes can be recognised, sometimes for several days after transfusion. The normal corpuscles can be readily distinguished by their regular shape and size and from the uniform way in which they are stained; they form a marked contrast to the patient's corpuscles, which usually show the variations in size, shape and staining reactions typical of pernicious anaemia.

Occasionally signs of reaction on the part of the bone marrow appear soon after transfusion. This favourable indication was recognised in case 2. Prior to the transfusion the patient had shown no tendency to react to treatment and the bone marrow was apparently exhausted. It was noted at the time that few nucleated red cells could be seen, but two hours after transfusion, when the films were again examined, the nucleated red corpuscles were numerous, and one or more normoblasts could be found in every field of the microscope. The patient had been gradually sinking and had been unable to take arsenic. Three days later both the general condition and the blood count were improved, and this occurred before arsenic was resumed. It was probable therefore that the appearance of normoblasts in the blood was a/

a sign of fresh stimulation of the bone marrow by the transfusion of blood.

The later changes in the blood films of the cases treated by transfusion varied with the progress of the case. When the symptoms failed to improve the blood films remained unaltered, but in cases in which a remission followed transfusion the type of cells gradually became more normal, poikilocytosis was less marked and normoblasts were more frequently observed than megaloblasts.

#### Comments on the Results Recorded.

It can be definitely stated that, although transfusion may cause a remission of symptoms, it cannot cure a case of Pernicious Anaemia or alter in any material way the nature of the disease. The most that can be expected is that a remission may be encouraged when it had failed to set in before.

Considering the cases as a whole, it can be stated that a definite remission was started by transfusion on thirteen of the twenty-three occasions (56.5%) on which it was employed.

In four cases arsenic was not given until some time after the transfusion and was then the main factor in the remission which followed.

After nine of the transfusions a fresh period of remission was initiated when arsenic had previously failed.//



failed. (47.3%).

Chief stress must be laid on the effects of transfusion in starting a remission when the bone marrow is apparently exhausted and when arsenic has proved useless.

The chances of recovery are greater if the patient is transfused before death is imminent and this is brought out by the following figures..

- A. After eight transfusions done as a last resort when the patients were regarded as hopeless and dying, the transfusion definitely saved life and started a fresh remission in three cases (37.6%).
- B. After eleven transfusions done when the patient was seriously but not critically ill, and had failed to benefit by arsenic there was a fresh remission in six cases. (54.5%)

These figures, therefore, show that the chances of success are greater if transfusion is not postponed till the patient is in extremis. The results of transfusion will always be uncertain and it is impossible to foretell whether a case will benefit or not. Acute and toxic cases associated with marked pyraëxia are little likely to benefit. The chief advantage of transfusion is that it offers a chance of restoring health to stationary or progressive cases and even to patients who are otherwise hopeless//

hopeless and even in an apparently dying condition. The fact that the longest survival recorded in my series of cases was rallied from an unconscious and critical condition by transfusion indicates that the question of transfusion should be seriously considered when all other attempts at treatment have failed. It must be granted at the same time that the prospects of benefit for any length of time are not great.

The theoretical grounds for transfusion are less satisfactory in this disease than in the case of primary haemorrhage or even in secondary anaemia. The etiology of pernicious anaemia is still obscure, and, except in a few cases, it is impossible to detect the source of the toxæmia which presumably is the cause of the symptoms. The treatment of suspected foci of infection in the mouth and intestinal tract does not seem so far to have influenced greatly the inevitable progress of the disease. Different views are held regarding the explanation of the changes characteristic of pernicious anaemia and particularly as to whether the bone marrow is primarily, or secondarily, affected. According to some authorities haemolysis of the red blood corpuscles is unduly active, and the increase of red marrow is compensatory. Those who support the alternative theory regard the marrow//

marrow as being primarily affected; the active destruction of corpuscles is explained by the formation of immature and fragile cells abnormally susceptible to the haemolytic activities of the organs concerned with the removal of effete corpuscles.

It is obvious that, if the former theory is correct, the life of transfused corpuscles would be soon ended. My observations prove that a large proportion of the transfused corpuscles are maintained intact for several days after transfusion, and they therefore support the theory that the excessive haemolysis, which occurs in progressive cases of pernicious anaemia, is due to the impaired quality of the corpuscles formed in the marrow rather than to exalted haemolytic properties of the serum and organs such as the liver and spleen. There is therefore no contra-indication to transfusion through the belief that the engrafted corpuscles are likely to be rapidly destroyed and functionless.

The results achieved will be more uniform if gross incompatibilities of the blood of the donor and recipient have been excluded by preliminary tests. No disaster followed in any of my cases from the omission of preliminary tests, but I do not wish to minimise the risks of using untested blood for transfusion, and must attribute my own immunity from mishaps/

mishaps chiefly to good fortune. In my recent work I have always, whenever circumstances permitted, employed the agglutination test before transfusion.

The method of transfusion is, I believe, of special importance in a condition such as pernicious anaemia where the blood is abnormal. No method can give more satisfactory results than direct transfusion from artery to vein, but the advantages of direct transfusion are not sufficiently great to make it preferable to the simpler method of indirect transfusion, from vein to vein, which entails less sacrifice on the part of the donor. It is not advisable to use citrated blood or sodium phosphate in pernicious anaemia when methods of transfusing unmodified blood are available. A large amount of blood is not required and the benefit derived is certainly not in proportion to the amount transfused. The dangers of over-transfusion are greater in pernicious anaemia than in cases of recent haemorrhage where the volume of the blood has been suddenly diminished. The fatty and degenerative changes in the myocardium also limit greatly the degree of strain, associated with an increase of blood pressure, which the heart can withstand. It is convenient, although not necessary, to measure the amount of blood transfused. From 300 to 450 ccs. of blood can/



can raise the haemoglobin per centage from 20 to 30, and this amount is not likely to cause inconvenience either to the donor or the recipient. The chief advantage of measuring the blood is that the donor is not likely to suffer by sacrifice of an unnecessary amount.

The question of repeating transfusion may have to be considered, either when a first transfusion has failed to produce the desired improvement, or when the symptoms relapse. The repetition of transfusion was certainly successful in two of my cases and it might quite well be considered more often.

While there is no doubt that transfusion of blood has a favourable influence in certain cases, it is difficult to offer a satisfactory explanation of its therapeutic action. As the duration of transfused corpuscles in the circulation of the recipient seldom exceeds a few days, the advantage of introducing a comparatively small amount of blood is not very obvious. It is of course apparent, in cases where the corpuscles are reduced to a minimum, that transfusion of blood might temporarily supply the deficiency and improve oxygenation sufficiently to prolong life for a short time. If transfusion had no other effect than this its advantages would be small indeed. The transfusion of normal blood could/

could hardly be expected to have any specific action on the cause of the anaemia. It has been suggested that fresh serum will dilute or neutralise the toxins in circulation and it is possible that this may be the case. The only way in which the symptoms of pernicious anaemia can be permanently improved is by the stimulation of the bone marrow, and one of the remarkable features of the disease is the tendency for a remission of the symptoms to occur, either spontaneously or as a result of treatment. Although remissions do occasionally occur, even in apparently hopeless cases, the chances of a spontaneous recovery, when the bone marrow is exhausted, diminish with the lapse of time. The bone marrow must suffer along with the other organs from the effects of prolonged anaemia. The toxæmia affects the bone marrow primarily, but, finally, a vicious circle may ensue and the persistence of the anaemia thereafter may in its turn diminish the natural tendency of the bone marrow to react. There is no doubt that under such circumstances the transfusion of blood does sometimes act as a stimulus to the marrow. Apart from the possible neutralisation of toxin, the most reasonable explanation of the beneficial effects of transfusion is that the bone marrow, sharing in the temporary improvement//

improvement in the general condition of the patient which immediately follows transfusion, is in a better condition to react than it was before. There was little evidence in my series to show that transfusion by itself was sufficient to cause a continued stimulation of the marrow, and a progressive reduction of the anaemia, without the coincident administration of arsenic. Apart from the cases where transfusion is employed as an emergency procedure, its chief value is that in stationary or progressive cases it may stimulate the marrow in such a way that arsenic again becomes effective and the patient's health is improved for a variable period till a subsequent relapse occurs.

From the facts observed in this series of twenty-one cases I feel justified in drawing the following conclusions..

C O N C L U S I O N S .

1. Transfusion of blood is of considerable value in cases of Pernicious Anaemia which have failed to respond to all the usual medical measures. It may alleviate, but cannot cure, such cases.
2. The ideal method of transfusion is either direct, from artery to vein, or, preferably, indirect transfusion from vein to vein. Anticoagulant substances should not be used when methods of transfusing unmodified blood are available.
3. A large amount of blood is unnecessary, owing to the risks of over-transfusion, and to the fact that the benefit conferred by transfusion is not necessarily in proportion to the volume of blood received.
4. A repetition of transfusion should be considered when the symptoms relapse or if the first transfusion fails to produce the desired effect.
5. The dangers associated with transfusion are small when the modern technique for transfusion is used, and especially if preliminary tests have been made to exclude the risks of haemolysis.



6. Transfusion is not to be regarded as an alternative to other forms of treatment, but as a therapeutic agent in reserve, available when the usual measures have failed.
7. The benefit resulting from transfusion may be only slight and temporary, or it may be continuous and a fresh period of remission from the anaemia may be initiated.
8. The prospects of benefit are greater if the transfusion is not postponed till the patient is critically ill, and in immediate danger of dying.
9. Even in apparently exhausted cases, regarded as hopeless and whose death appears to be imminent, transfusion occasionally will resuscitate the patient in a remarkable manner.
10. Transfusion will initiate a fresh remission in 39.1% of cases in which the anaemia has been progressive or has failed to respond to medical treatment including arsenic.
11. When the patients are critically ill at the time of transfusion, having failed to respond to treatment including arsenic, a fresh remission follows in 37.6% of the cases.

12. When the patients are seriously, but not critically, ill at the time of the transfusion, having failed to respond to treatment including arsenic, a fresh remission follows in 54.5% of the cases.
13. The results of transfusion are always uncertain in any given case.
14. Cases of an acute type and cases with marked pyrexia, or a history of haemorrhages, are least likely to benefit.
15. The immediate effects of transfusion are often striking. Signs of improvement are noted in the colour, mental alertness, pulse, blood pressure and in the appetite. The patient frequently feels better and stronger.
16. Symptoms of nausea and vomiting are occasionally almost at once relieved and the patient is better able to take nourishment.
17. Arsenic occasionally is better tolerated and frequently is more effective after transfusion.
18. The onset of a remission following transfusion is due to reactions of the bone marrow.
- 19.//

19. Fresh activity on the part of the bone marrow may possibly be due to dilution of toxin, or to direct stimulation of the marrow, but is more probably a result of the general improvement in nutrition, following upon transfusion and the more effective exhibition of arsenic.
20. There is little evidence that a single transfusion of blood will continue to stimulate the bone marrow and to diminish the anaemia, unless arsenic is continued.
21. The advisability of transfusion should be considered, but the results are not sufficiently consistent or permanent to justify it being urged, in all cases of Pernicious Anaemia which are stationary, progressive or critically ill, in spite of the usual means of treatment.

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